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Association between Triglyceride Glucose Index and Arterial Stiffness in the Japanese Population: A Secondary Analysis of Cross-Sectional Study

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ABSTRACT

The trigly cerise glucose (TyG) index has been regard edams a reliable alternative biomarker of insulin resistance (IR). However, there are limited studies that have been carried out regarding the association between the TyG index and arterial stiffness. Therefore, the main objective of this research was to explore the correlation between the TyG index and arterial stiffness. This cross-sectional study recruited 912 Japanese whose age ranged from 24 to 84 years from a health checkup project. all subjects were divided into three groups. Multivariate linear regression demonstrated that the TyG index exhibited an independent positive association with baPWV (β0.34, 95%confidence interval [CI]0.08–0.59). Consistently, in the multivariable logistic regression, each unit increase in the TyG index increased the odds of having a higher prevalence of elevated arterial stiffness by 65% (OR 1.65, 95%CI1.08–2.54). According to the restricted cubic spline, the correlation between baPWV and TyG index was linear and did not find a threshold or saturation effect. Subgroup analyses revealed that the relationship between the TyG index and baPWV stably existed in different subgroups after adjusting covariates. In Conclusion, The TyG index is independently associated with arterial stiffness.

Abbreviations: TYG Index: Triglyceride Glucose Index; BAPWV: Brachial Ankle Pulse Wave Velocity; IR: Insulin Resistance; CVD: Cardiovascular Disease; BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; GGT: γ-Glutamyl Transpeptidase; FPG: Fasting Plasma Glucose; TG: Triglyceride; TC: Total Cholesterol; HDLC: High Density Lipoprotein Cholesterol; LDLC: Low Density Lipoprotein Cholesterol; ALT: Alanine Aminotransferase; AST: Aspartate Transaminase; EGFR: Estimated Glomerular Filtration Rate; HOMA-IR: Homeostasis Model Assessment For Insulin Resistance

Introduction

Arterial stiffness increases with age and has been considered as an independent predictor of age-associated morbidity and mortality [1,2].Currently, brachial-ankle pulse wave velocity (baPWV), due to its repeatability and simplicity [3,4], is an easily applicable and extensively used parameter for clinical assessment of arterial stiffness in large population studies [3].A number of studies over the past decade have suggested that increased arterial stiffness was correlated with an increase the risk of hypertension [5],diabetes [2], stroke [4], coronary calcification [3], total cardiovascular events, and all-cause mortality [6].Insulin resistance (IR), a resistance of target tissues to insulin stimulation, is regarded as a critical role in glucose and lipid metabolism [7]. Previous studies demonstrated that IR may play an important role in arterial stiffness progress and cardiovascular disease (CVD) [8-11]. As a general rule, the reference standard to quantify insulin sensitivity is the euglycemic-hyperinsulinemia clamp technique [12]. However, this method is costly, time-consuming, and impractical in clinical work [13]. The homeostasis model assessment for IR (HOMA-IR) is more regularly applied to assess IR, which utilizes glucose and insulin levels after overnight fasting [14]. Recently, the TyG index has been proposed as a persuasive marker of IR [15]. In addition, it has been reported that the TyG index is better than HOMA-IR in terms of assessing IR in clinical practice [16,17]. Several research have indicated that elevated TyG index was correlated with an increased risk of arterial stiffness [18-22]. As mentioned above, the TyG index is a reliable biomarker of IR, which is readily available in clinical settings or large-scale medical checkups. It almost certain that several researchers have observed TyG index is markedly correlated with the risk of arterial stiffness in China [14,23,24], Korea [21,25], Vietnam [26], and Brazil [27]. However, little attention has been focused on the study of TyG index and arterial stiffness in Japan. Therefore, we aimed to examine the correlation between arterial stiffness and the TyG index in a Japanese population.

Methods

Data Source

Researchers are allowed to download freely the original study data from theDRYAD database (http://www.Datadryad.org/).Wecited the data from the dryad database package (Takuya Fukuda, et al. [28]). Details can be acquired from the following: Association between serum γ-glutamyl transpeptidase and atherosclerosis: a population-based cross-sectional study (data set. doi:10.5061/dryad.m484p). This dataset material contained a number of variables: sex, age,body mass index (BMI), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), γ-glutamyl transpeptidase (GGT), fasting plasma glucose (FPG), triglyceride(TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), aspartate transaminase (AST), alanine aminotransferase (ALT), estimated glomerular filtration rate (eGFR), brachial-ankle pulse wave velocity (baPWV), ankle-brachial index (ABI), uric acid, smoking status, regular exercise, fatty liver, alcohol consumption.

Study Population

There was a physical examination programme, including pulse wave velocity, in the Murakami Memorial Hospital (Gifu, Japan). The project aims to improve public health by early detecting early diseases and assessing their potential risk factors. Participants received a health checkup between March 2004 and December 2012. Altogether there are 912 participants (592 male and 320 female) were enrolled based on the following exclusion criteria:

1. The participants had positive hepatitis B antigen and/or positive hepatitis C antibody.
2. The participants had receiving medication
3. The participants received hormone replacement therapy
4. The participants had oral contraceptives and were pregnant
5. The participants' ABI was <0.95. The study was carried out in line with the Declaration of Helsinki. All participants signed an informed consent form.

Data Collection and Measurements

All participants completed a standardized self-administered questionnaire to obtain the medical history and lifestyle factors, including smoking status, alcohol habits, and physical activity. For example, a drinking history was investigated by the type of alcohol and averaged ethanol intake per week during the prior month and then divided into four groups: non or minimal alcohol consumption, <40 g/week; light alcohol consumption, 40–140 g/week; moderate alcohol consumption, 140–280 g/week; and excess alcohol consumption, >280 g/week [29-31].Smoking history was divided into three classes: never, former and current smoker. Regular exercise was defined as participating in any sport regularly at least once a week [32]. Fasting blood specimens were collected from all participants after an overnight fast. The baPWV was determined using (La-Lb)/DTba. The lengths from the participant's suprasternal notch to the brachium (Lb) and to the ankle (La) were measured respectively based on their height. The delay time from the ascending point of the brachial waveform to each ankle waveform (DTba) was determined automatically [28]. According to a recent study [23], the definition of increased baPWV was considered to be a baPWV value that exceeds the 75th percentile. The diagnosis of fatty liver was based on the results of the abdominal ultrasonography performed by experienced gastroenterologists [31] of the four known criteria, fatty liver was diagnosed when characteristic features of "bright liver" with evident contrast between the hepatic and renal parenchyma were seen in the US [33]. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. The estimated glomerular filtration rate (eGFR) was calculated by the formula which the Japanese Society of Nephrology developed: eGFR=194×Cr−1.094×age−0.287 (mL/min/1.73 m^2) for males and was multiplied by a correction factor of 0.739 for females [34]. The TyG index was determined using ln [triglycerides (mg/ dL) × glucose (mg/dL)/2] [35].

Statistical Analysis

Continuous variables are displayed as mean with standard deviation (SD) or interquartile range (IQR). Categorical variables are summarized as proportions. For baseline characteristics analysis, the statistical differences among tertiles of the TyG index were tested with One-way ANOVA or Kruskal-Wallis H test for continuous variables and chi-square test for categorical variables. Increased baPWV was considered a baPWV value exceeding the 75^{th} percentile, which was greater than 15.16 m/s in the present study. The relationships of baPWV with the TyG index, sex, age, BMI, SBP,or other variables were examined by univariate linear regression analyses. Multivariate linear models and multivariate logistic regression models were used to determine the independent association of the TyG index with baPWV and increased baPWV. Three models were set up with adjustment for potential confounding variables:

1. **Model 1**: Adjusted for sex and age
2. **Model 2**: Adjusted for variables in model 1 plus BMI, SBP, HDL-C, TC, eGFR, Fatty liver, alcohol consumption (continuous)
3. **Model 3**: Adjusted for variables in model 2 plus uric acid, regular exercise, Current smoking.

In the regression analyses model, these potential confounders were chosen on the basis of and a more than 10% change in effect estimates. A generalized additive model (GAM) and a fitted smoothing curve (penalized spline method) were used to identify non-linear relationships because the TyG index was a continuous variable. In addition, interaction and stratified analyses were performed according to sex, age (<60vs.≥60 years), SBP (<130 vs.≥130 mmHg), BMI (<25vs.≥25 kg/m^2), LDL-C (<126 vs.≥126 mg/dL), Alcohol consumption (<40 vs.≥40g/week), current smoking (yes vs. no), regular exercise (yes vs.no), fatty liver (yesvs.no), eGFR (<60 vs.≥60 mL/min/1.73 m2). All statistical analysis was conducted with the statistical software R (http://www.R-project.org, The R Foundation) and Free Statistics analysis platform. A 2-tailed P<0.05 was considered significant.

Result

Demographic and Clinical Characteristics

Descriptive statistics and percentages were used to summarize demographic and clinical characteristics listed. The average age of the 912 participants was 51.1±9.6 years, and 592 were male (64.9%). The mean TyG index was 8.30±0.7, and the mean baPWV was 14.20±2.5m/s. Compared to the lowest tertiles of the TyG index, participants in the higher tertiles were more frequently men, smokers, drinkers and had fatty liver disease (all P value<0.05); had lower levels of HDL-C; and had higher BMI, blood pressures, fasting glucose levels, TG, TC, LDL-C, AST, ALT, uric acid.

Univariate Analysis for baPWV

The results obtained from the preliminary analysis of univariate linear regression analyses. The baPWV was significantly associated with sex, age, TC, TG, FPG, SBP, DBP, AST, ALT, eGFR, uric acid, and TyG index, but not BMI, regular exercise, alcohol consumption, and current smoking.

Association of TyG Index with baPWV and Elevated baPWV

To sum up, significant positive correlations were observed between the TyG index and baPWV the rise in the baPWV is paralleled by an increase in TyG index. According to the estimation from regression coefficients indication, each unit increment in TyG index, baPWV is changed in 0.3 m/s (95%CI 0.08-0.59, P =0.009). To further probe for more details about the relationship between the two, we categorize the TyG index into tertiles and use the lowest tertiles as a reference group. After adjustment for different confounders, there is a significant positive correlation between the TyG index and BaPWV according to three models (model 1–3). Compared to the lowest tertiles of the TyG index, the second and highest tertiles were significantly associated with a 0.20 m/s (95%CI -0.1–0.51, P =0.191) and 0.44 m/s (95%CI 0.06–0.82, P=0.024) increase in baPWV, respectively. Consistently,the fully adjusted model indicated that per 1-unit increase in the TyG index increased the odds of having a higher prevalence of increased arterial stiffness by 65% [OR1.65; 95%CI1.08–2.54;P<0.05]. Compared to the first tertiles of the TyG index, the second and third tertiles were correlated with a 63% [OR 1.6; 95%CI 0.96–2.75; P=0.068] and 78% [OR 1.78; 95%CI 0.93–3.39; P=0.080] higher prevalence of increased arterial stiffness, respectively.

Subgroup Analyses

In addition, we conducted a subgroup analysis for TyG index and baPWV based on the potential modifiers including age, sex, BMI, SBP, HDL-C, TC, eGFR, Fatty liver, alcohol consumption (continuous), uric acid, regular exercise, and Current smoking, if not be stratified. There was consistent relationship identified between TyG index and baPWVin the subgroups: sex (male vs female; P for interaction=0.82),age (<60 vs.≥60 years; P for interaction=0.06), SBP (<130 vs.≥130 mmHg; P for interaction=0.49), BMI (<25 vs.≥25 kg/m^2; P for interaction=0.44), LDL-C (<126 vs.≥126

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mg/dL; P for interaction=0.64), Alcohol consumption (<40 vs.≥40g/week; P for interaction=0.48), current smoking (yes vs. no; P for interaction=0.12), regular exercise (yes vs. no; P for interaction=0.88), fatty liver (yes vs. no; P for interaction=0.54), eGFR (<60 vs.≥60 mL/min/1.73 m^2; P for interaction=0.64). The stratified analysis indicated that the association between TyG index and baPWV stably existed in the different subgroups.

Discussion

We investigated the association between the TyG index and arterial stiffness estimated by baPWV in the Japanese population. The research suggests that a positive correlation was found between the TyG index and arterial stiffness after covariates adjustment. The results were stable in the stratified analysis according to sex, age, BMI, SBP, LDL-C, current smoking, alcohol consumption, regular exercise, fatty liver, eGFR. IR has been considered to play a critical role in several metabolic diseases [36-38]. The reference standard to evaluate IR is the euglycemic-hyperinsulinemia clamp test [39], but this method is costly, invasive, and difficult to perform in clinical settings. Thus, the development of HOMA-IR is provided an alternative and more convenient approach for assessing IR and is widely applied in clinical practice [40]. Recently, a number of studies have confirmed that the TyG index is closely correlated with IR and considered as urrogate biomarker of IR when compared with using the euglycemic-hyperinsulinemia clamp test and HOMA-IR [35,41,42]. Furthermore, some research has established that the TyG index showed better predictive value for IR than HOMA-IR [17,43]. A cross-sectional study of 2560 Korean participants was carried out by Won, et al. [21] revealed that the TyG index (β 0.158, P< 0.05) is positively associated with arterial stiffness in a relatively healthy population. Another cross-sectional research with 2830 elderly participants in a Northern Shanghai Study of China also showed that compared to the lowest quartile of TyG index, participants in the highest quartile were associated with an increased OR for baPWV > 1800 cm/s (OR 1.39; 95%CI 1.05–1.84; P for trend< 0.05) after adjustment for sex, age, waist circumference (WC), BMI, smoking status, hypertension ,diabetes, family history of premature CVD, LDL-C, HDL-C, insulin therapy and statin therapy [20].

Our results are inconsistent with the previous research. In this study, we found that after adjusted for potential covariates, the TyG index was still correlated with baPWV (TyG as a continuous variable: β 0.44, 95%CI 0.06–0.82, P=0.024, and as categorical variables: OR 1.65, 95% CI 1.08–2.54, P =0.021). Our subgroup analysis indicated that the relationship between TyG and baPWV stably existed, and we did not find significant interaction effects in the different subgroups. Li, et al. [23] recently conducted a study of 4718 Chinese H-type hypertensive patients and demonstrated that the TyG index is independently positively associated with arterial stiffness, using the multivariate linear regression models and multiple logistic analyses (β 1.02, 95%CI 0.83–1.20; OR 2.12, 95%CI 1.80–2.50, respectively). Interestingly, they observed that a stronger association between the TyG index and baPWV were identified in men (P for interaction = 0.02). However, Nakagomi, et al. [44] found that the correlation between the TyG index and elevated baPWV (>75^{th} percentile) was more robust in women rather than in men. The inconsistent and contradictory results might be attributed to the difference in age. As a result, further studies are still necessary to explore the correlation of the TyG index and arterial stiffness, especially to make a sex sensitivity analysis. Although the mechanism responsible for the relationship between the TyG index and arterial stiffness is elusive, it may be linked to IR. It has been assumed that IR is correlated with persistent, low-degree inflammation [45].

Besides, IR may result in endothelial injury and led directly to endothelial barrier dysfunction [46], an essential pathophysiological process in the progression of atherosclerosis. Alternatively, IR has been associated with increased activity of the sympathetic nervous system [47]. In summary, the TyG index was positively associated with arterial stiffness after adjustment for different covariates. Our study does present several limitations: First, our participants were Japanese and enrolled at one physical examination center. Therefore, the generalizability of the results may be limited. Second, given the cross-sectional design, no causal inferences can be established. Third, raw data were limited. Our study population was relatively small, which might have an influence on the reliability of results. Fourth, because the raw data did not provide information on insulin levels, we couldn't calculate the HOMA-IR and failed to compare the role between the TyG index and HOMA-IR. However, the direct correlation between them was well-established as previously described. Despite these limitations, the present study identifies the independent impact of the IR estimated by the TyG index on arterial stiffness.

Conclusion

We demonstrated a significant positive association between the TyG index and arterial stiffness estimated by baPWV in the Japanese population. The data indicate that the TyG index may serve as a simple and useful tool for arterial stiffness risk assessment in daily clinical practice. Further research is required to explore the mechanism of this relationship.

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Disclosure

The authors declare that the research received no external funding and declare no conflict of interest.

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