Association between Triglyceride Glucose Index and the Risk of Peripheral Artery Disease

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Abstract

Background The triglyceride glucose (TyG) index has been used as a simple surrogate marker of insulin resistance, an independent predictor of atherosclerotic vascular diseases. However, few studies have investigated the relationship between the TyG index and peripheral artery disease (PAD).

Methods A total of 3375 participants with completed TyG and ankle brachial pressure index (ABPI) records were enrolled from the National Health and Nutrition Examination Survey (NHANES) 1999-2004. The TyG index was calculated as ln[triglycerides (mg/dL)×glucose (mg/dL)/2], and the presence of PAD was defined as ABPI ≤ 0.9.

Results The participants were 60.1±12.8 year old and 51.3% (1730) were male. The prevalence of PAD was 7.1% (238). Compared with the reference lowest quartile of TyG index, the highest quartile was associated with 1.66-fold (odds ratio [OR], 95% confidence interval [CI] 1.15-2.43; p=0.008) risk of PAD. After adjusted for sociodemographic, lifestyles, and cardiometabolic factors, the multivariate-adjusted OR and 95% CI were 1.55 (1.03-2.37; p=0.039) or participants within the highest quartile. TyG index was also independently and linearly associated with higher presence of PAD (OR 1.27 [1.02-1.56]; p=0.027). Subgroup analysis showed that the association between TyG index and the risk of PAD was still consistent across groups except for obesity.

Conclusions Higher TyG index was significantly associated with the higher risk of PAD, which could be a marker of PAD.

Background

Cardiovascular disease (CVD) is a leading cause of morbidity and mortality worldwide[1]. Peripheral artery disease (PAD), defined as ankle-brachial pressure index (ABPI) ≤ 0.9, has been established as an independent marker for atherosclerotic vascular diseases [2] and a predictor for all-cause mortality and cardiovascular event [3]. Screening the risk factors of PAD was necessary to reduce the complications.

The triglyceride glucose (TyG) index has been regarded as a reliable surrogate marker of insulin resistance (IR)[4, 5], characterized by poor insulin sensitivity in the peripheral tissues[6]. There were growing evidences to show that IR contributed to vascular remodeling and increased vascular calcification [7, 8], contributing to the risk of cardiovascular diseases and mortality[9]. Many studies have identified TyG index was associated with cardiovascular diseases [10, 11]. However, few study has investigated the association between the TyG index and the risk of PAD in general population.

In the present study, we evaluated the association between the TyG index and the risk of PAD in general population.

Methods

Study population

The study used data from National Health and Nutrition Examination Survey (NHANES) between the periods of 1999 to 2004, a nationwide survey conducted by the National Center of Health Statistics (NCHS). After excluding participants with missing data on triglyceride (328) and glucose (3484) from 7187 participants with ABPI records, 3375 participants were enrolled in our analysis (Figure 1). The study was approved by the institutional review board of NCHS and all participants provided written informed consent.
Exposure variable and outcomes

The TyG index was determined as ln (triglycerides [mg/dL]×glucose [mg/dL]/2). Plasma triglyceride was measured enzymatically using Roche Modular P chemistry analyzer and fasting glucose was measured by an enzymatic method. The ABPI exam was performed by trained health technicians in the mobile examination center. Participants lie supine on the exam table during the exam. Systolic pressure is measured on the right arm (brachial artery) and both ankles (posterior tibial arteries). Systolic blood pressure is measured twice at each site for participants aged 40–59 years and once at each site for participants aged 60 years and older. The ABPI was automatically calculated by the computer system and verified by NCHS. The presence of PAD was defined as any of left or right ABPI ≤ 0.9.

Covariates collection

The baseline characteristics of participants were acquired by questionnaires and examinations, including sociodemographic (gender, age, race, and educational level), lifestyle information (physical activity and smoking status), and medications use (hypoglycemic drugs and lipid-lowering drugs). Systolic blood pressure and diastolic blood pressure were measured by physical examination. Body mass index (BMI) was calculated as body weight divided by height squared. Race was classified as non-Hispanic white, non-Hispanic black, Mexican American, other Hispanic or others. Education level was categorized as less than high school, high school, equivalent and college or above. Smoking status were defined as current, past and never. Physical activity status was classified as vigorous, moderate and inactive. Vigorous physical activity was defined as an activity that greatly increases the breathing or heart rate. Moderate physical activity was defined as an activity that causes small increases in breathing. Multiple imputation using predictive mean matching (PMM) was performed for covariates with missing values.

Statistical Analysis

Continuous variables were described as the mean ± standard deviation while categorical variables were presented as numbers and proportions (percentage). Differences between groups were explored by one-way analysis of variance (ANOVA) or chi-square tests. Multivariate logistic regression models were used to estimate odds ratios (ORs) and 95% confidence interval (CI) between TyG quartile and PAD. Multivariate linear regression models were used to explore the risk of PAD per one-unit increase of TyG index. Model 1 was not adjusted. Model 2 was adjusted for age, gender, and race. Model 3 was adjusted for age, gender, race, education level, BMI, smoking status, and physical activity. Model 4 was adjusted for age, gender, race, education level, BMI, smoking status, physical activity, systolic blood pressure, diastolic blood pressure, hypoglycemic drug, and lipid-lowering drug. Subgroup analyses was performed to explore the interactions modifying the relationship. All statistical analyses were performed using R version 3.6, and P<0.05 was considered as statistically significant.

Results

Participants were stratified into four groups according to their TyG quartiles. The baseline characteristics of the study population were shown in Table 1. The highest TyG quartile tended to have more percentage of male,
Mexican American, and hypoglycemic drugs users. In addition, the prevalence of PAD was significantly increased across TyG quartiles.
| Variable                | Overall (n = 3375) | Q1 (n = 844) | Q2 (n = 848) | Q3 (n = 837) | Q4 (n = 846) | \( P \) value |
|-------------------------|--------------------|--------------|--------------|--------------|--------------|---------------|
| Male (%)                | 1730 (51.3)        | 379 (44.9)   | 443 (52.2)   | 411 (49.1)   | 497 (58.7)   | < 0.001       |
| Age, years              | 60.1 (12.8)        | 57.4 (13.3)  | 60.4 (13.4)  | 61.8 (12.4)  | 60.9 (11.8)  | < 0.001       |
| Race (%)                |                    |              |              |              |              | < 0.001       |
| Non-Hispanic white      | 1879 (55.7)        | 457 (54.1)   | 483 (57.0)   | 482 (57.6)   | 457 (54.0)   |               |
| Non-Hispanic black      | 544 (16.1)         | 231 (27.4)   | 138 (16.3)   | 95 (11.4)    | 80 (9.5)     |               |
| Mexican American        | 728 (21.6)         | 113 (13.4)   | 176 (20.8)   | 186 (22.2)   | 253 (29.9)   |               |
| Others                  | 224 (6.6)          | 43 (5.1)     | 51 (6.0)     | 74 (8.8)     | 56 (6.6)     |               |
| Education (%)           |                    |              |              |              |              | < 0.001       |
| Less than high school   | 1117 (33.1)        | 239 (28.3)   | 279 (32.9)   | 275 (32.9)   | 324 (38.3)   |               |
| High school or          | 774 (22.9)         | 175 (20.7)   | 190 (22.4)   | 198 (23.7)   | 211 (24.9)   |               |
| equivalent              |                    |              |              |              |              |               |
| College or above        | 1484 (44.0)        | 430 (50.9)   | 379 (44.7)   | 364 (43.5)   | 311 (36.8)   |               |
| BMI, kg/m2              | 28.37 (5.54)       | 26.77 (5.45) | 27.83 (5.54) | 29.23 (5.63) | 29.67 (5.06) | < 0.001       |
| Smoking (%)             |                    |              |              |              |              | < 0.001       |
| Never                   | 2337 (69.2)        | 622 (73.7)   | 568 (67.0)   | 619 (74.0)   | 528 (62.4)   |               |
| Past                    | 142 (4.2)          | 25 (3.0)     | 30 (3.5)     | 36 (4.3)     | 51 (6.0)     |               |
| Current                 | 896 (26.5)         | 197 (23.3)   | 250 (29.5)   | 182 (21.7)   | 267 (31.6)   |               |
| Activity (%)            |                    |              |              |              |              | < 0.001       |
| Inactive                | 258 (7.6)          | 63 (7.5)     | 68 (8.0)     | 59 (7.0)     | 68 (8.0)     |               |
| Moderate                | 1883 (55.8)        | 430 (50.9)   | 449 (52.9)   | 480 (57.3)   | 524 (61.9)   |               |
| Vigorous                | 1234 (36.6)        | 351 (41.6)   | 331 (39.0)   | 298 (35.6)   | 254 (30.0)   |               |
| Hypoglycemic drugs      | 1953 (57.9)        | 454 (53.8)   | 421 (49.6)   | 526 (62.8)   | 552 (65.2)   | < 0.001       |
| Lipid-lowering drugs    | 2497 (74.0)        | 601 (71.2)   | 661 (77.9)   | 604 (72.2)   | 631 (74.6)   | 0.008         |

Data are presented as mean (SD) or n (%). Q1: TyG index < 8.34; Q2: 8.34 ~ 8.74; Q3: 8.74 ~ 9.17; Q4: > 9.17. BMI, body mass index; BP, blood pressure.
| Variable          | Overall (n = 3375) | Q1 (n = 844) | Q2 (n = 848) | Q3 (n = 837) | Q4 (n = 846) | P value |
|-------------------|--------------------|--------------|--------------|--------------|--------------|---------|
| Systolic BP, mmHg | 131.63 (21.04)     | 129.57 (21.38)| 130.18 (21.11)| 133.33 (21.50)| 133.44 (19.89) | < 0.001 |
| Diastolic BP, mmHg| 71.95 (14.40)      | 72.27 (13.69)| 71.63 (13.86)| 71.77 (15.33)| 72.14 (14.68) | 0.772   |
| Triglycerides, mg/dL | 151.6 (154.3)   | 66.2 (14.9)  | 104.6 (17.0) | 148.7 (27.0) | 286.9 (256.8) | < 0.001 |
| Glucose, mg/dL    | 109.5 (38.2)       | 94.3 (11.6)  | 100.3 (15.3) | 106.5 (20.9) | 136.9 (62.8)  | < 0.001 |
| TyG               | 8.79 (0.68)        | 8.01 (0.25)  | 8.54 (0.12)  | 8.94 (0.12)  | 9.68 (0.53)   | < 0.001 |
| PAD               | 254 (7.5)          | 48 (5.7)     | 59 (7.0)     | 70 (8.4)     | 77 (9.1)      | 0.039   |

Data are presented as mean (SD) or n (%). Q1: TyG index < 8.34; Q2: 8.34 ~ 8.74; Q3:8.74 ~ 9.17; Q4: >9.17. BMI, body mass index; BP, blood pressure.

The relationship between the TyG index and the presence of PAD was explored using multivariable linear regression. As shown in Table 2, per one-unit increase in the TyG index increased the risk of PAD (OR 1.27 [1.06–1.52]; p = 0.007). In a fully-adjusted model, the multivariate-adjusted OR and 95% CI was 1.27 (1.02–1.56; p = 0.027).
Table 2

Association of TyG index with the risk of PAD

| Cases | N   | Model 1 | Model 2 | Model 3 | Model 4 |
|-------|-----|---------|---------|---------|---------|
|       |     | OR (95%CI) | P       | OR (95%CI) | P       | OR (95%CI) | P       | OR (95%CI) | P       |
| Q1    | 47  | 844     | Ref     | -        | Ref     | -        | Ref     | -        | Ref     |
| Q2    | 54  | 848     | 1.24 [0.84, 1.84] | 0.284   | 1.12 [0.74, 1.70] | 0.58   | 1.03 [0.67, 1.57] | 0.905   | 1.07 [0.70, 1.65] | 0.743   |
| Q3    | 61  | 837     | 1.51 [1.04, 2.22] | 0.033   | 1.40 [0.94, 2.10] | 0.102  | 1.35 [0.89, 2.05] | 0.157   | 1.40 [0.92, 2.13] | 0.115   |
| Q4    | 76  | 846     | 1.66 [1.15, 2.43] | 0.008   | 1.69 [1.14, 2.53] | 0.010  | 1.52 [1.01, 2.32] | 0.047   | 1.55 [1.03, 2.37] | 0.039   |
| Continuous | 238  | 3375 | 1.27 [1.06, 1.52] | 0.007   | 1.33 [1.09, 1.62] | 0.005  | 1.29 [1.04, 1.59] | 0.018   | 1.27 [1.02, 1.56] | 0.027   |

Model 1 was unadjusted.

Model 2 was adjusted for age, gender, race and education level.

Model 3 was adjusted for age, gender, race, education level, BMI, smoking status, and physical activity.

Model 4 was adjusted for age, gender, race, education level, BMI, smoking status, physical activity, hypoglycemic drugs, lipid-lowering drugs, systolic BP, and diastolic BP.

OR, odds ratio; CI, confidence interval.

Multivariable logistic regression was used to evaluate the relationship between the TyG quartile and PAD using the first quartile as the reference. In unadjusted model 1, the highest TyG quartile was associated with a higher presence of AAC (OR 1.66 [1.15–2.43]; p = 0.008). In the fully adjusted model, the association still existed (OR 1.55 (1.03–2.37); p = 0.039).

Subgroup analysis for the associations between TyG index and the presence of PAD was shown in Fig. 2. The association was consistent across gender, elderly and race except for BMI (P for interaction = 0.002). The positive correlation between TyG index and PAD disappeared among obesity population.

Discussion

In this study, we investigated the association between the TyG index and PAD in general U.S. adults. We found that a higher TyG index were significantly associated with the prevalence of PAD. And this relationship disappeared in obesity individuals.

The TyG index has been proposed as an alternative surrogate marker for insulin resistance [12, 13]. Several studies demonstrated that the TyG index was positively correlated with HOMA-IR [14], and even has a better predictive value that HOMA-IR[15]. The TyG index was reported to be related to a higher risk of cardiovascular diseases and...
mortality[16]. In addition, some studies showed that the TyG index was significantly associated with the severity of coronary artery stenosis[17], artery stiffness [18] and vascular calcification [19]. Previous study found that the TyG index was an independent predictor of peripheral artery disease complexity based on a small sample size[20]. Our results further confirmed an independent association between the TyG index and the presence of PAD, and a higher TyG index increased the risk of PAD. Besides, we found that obesity was a factor affecting the relationship between TyG and PAD. The underlying interaction [21] required further research.

The mechanism underlying the relationship could be linked to IR. IR could lead to vascular inflammation and stiffness, which contributing to atherosclerosis of periphery artery [22, 23].

Some limitations existed in our study. Firstly, this was a cross-sectional study which could not infer causality. Second, the PAD was defined based on ABPI, which was lack of angiography examination.

Conclusions
In our study, we demonstrated that the TyG index was independently associated with the prevalence of PAD in U.S adults, which may serve as a potential predictive marker.

Declarations

Acknowledgements
Not applicable.

Authors’ contributions
B X and LN K designed the study. YH L performed the statistical analysis. MY W wrote the manuscript. All authors read and approved the final manuscript.

Competing interests
There is no conflict of interests.

Availability of data and materials
The datasets were available from NHANES 2013-2014 (https://www.cdc.gov/nchs/nhanes/index.htm).

Consent for publication
Not applicable.

Ethics approval and consent to participate
The study protocol was approved by NCHS Research Ethics Review Board (Protocol #2011-17).

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Figures
Participants with ABPI from NHANES 1999-2004 (n=7,187)

Participants with missing triglycerides (n=328)
Participants with missing glucose (n=3,484)

Participants with TyG index (n=3375) for analysis

Figure 1
The flow chart of participant selection.
| Subgroups | Cases | N    | OR(95%CI)       | P value |
|-----------|-------|------|-----------------|---------|
| Gender    |       |      |                 |         |
| Female    | 126   | 1645 | 1.40 [1.02, 1.90] | 0.448   |
| Male      | 128   | 1730 | 1.21 [0.89, 1.62] |         |
| Age       |       |      |                 | 0.835   |
| ≤60       | 46    | 1740 | 1.43 [0.90, 2.18] |         |
| >60       | 208   | 1635 | 1.31 [1.02, 1.69] |         |
| BMI       |       |      |                 | 0.002   |
| ≤30       | 183   | 2294 | 1.59 [1.23, 2.06] |         |
| >30       | 71    | 1081 | 0.81 [0.53, 1.20] |         |
| Race      |       |      |                 | 0.090   |
| Non–Hispanic white | 143 | 1879 | 1.23 [0.90, 1.65] |         |
| Non–Hispanic black | 54  | 544  | 1.75 [1.14, 2.65] |         |
| Hispanic  | 57    | 952  | 0.90 [0.56, 1.42] |         |

Figure 2

Subgroup analysis of the association between the TyG index and the presence of PAD.