Triglyceride Glucose Index Is Independently Associated With Aorta Intima-Media Thickness In Patients Without Clinical Manifestations of Cardiovascular Disease

Süleyman ÖZBİÇER (✉ suleymanozbicer@gmail.com)  
University of Health Sciences Adana City Training and Research Hospital

Gülhan Yüksel  
University of Health Sciences Adana City Training and Research Hospital

Örsan Deniz Urgun  
University of Health Sciences Adana City Training and Research Hospital

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Abstract

Background and Aims: Subclinical atherosclerosis begins to develop in the thoracic aorta early in life. Insulin resistance is a well-established risk factor for the development of atherosclerosis. The triglyceride-glucose (TyG) index is a reliable marker of insulin resistance regardless of glucose tolerance or obesity. We aimed to investigate the relationship between the TyG index and aortic intima-media thickness (IMT) in patients without diabetes mellitus and cardiovascular disease undergoing transesophageal echocardiography due to suspected structural heart disease.

Methods: One hundred twenty-two patients enrolled in the study between January 2021 and June 2021. Triglyceride-glucose index was calculated using fasting laboratory parameters, major cardiovascular risk factors and IMT of the thoracic aorta were recorded. Patients were divided into two groups according to their median IMT; patients with an IMT equal to or less than 1.42 mm were low IMT group, and higher than 1.42 mm were high IMT group.

Results: Triglyceride-glucose index were higher in the high IMT group (8.69 ± 0.59 vs. 8.37 ± 0.53, p=0.003). Triglyceride-glucose index was correlated with IMT (r=0.259, p=0.005) and in binary logistic regression analysis age and TyG was independently associated with having high IMT (β = 0.091, exp(B)=1.095 95%CI = 1.041 – 1.152, p<0.001 and β=1.726, exp(B)= 5.621 95%CI= 1.139- 27.728, p=0.034, respectively)

Conclusion: We found an independent relationship between TyG and IMT of the thoracic aorta, an early marker of subclinical atherosclerosis in patients without atherosclerotic cardiovascular disease. Therefore, the TyG index can be used to identify high-risk subjects among healthy subjects.

Introduction

For a long time, it has been known that atherosclerosis begins early, including in utero, and manifests itself with some pathological processes before it becomes clinically evident [1]. Recognition of the development of atherosclerosis before it becomes a clinical disease is essential in identifying individuals at risk and deciding on whom to apply intensive treatment regimens [2, 3]. However, the carotid artery is commonly used to measure preclinical atherosclerosis due to its availability; the thoracic aorta is affected by atherosclerosis earlier [4]. Patients who undergo transesophageal echocardiography for suspected structural heart disease such as atrial septal defect, ventricular septal defect, and thrombus in the left atrial appendage can be screened for markers of macroscopic disease and preclinical atherosclerosis of the thoracic aorta.

It is known that diabetes and metabolic syndrome, which are characterized by insulin resistance, accelerate the formation of all cardiovascular diseases, including coronary artery disease [2]. Numerous laboratory and anthropometric measurements have been proposed to measure insulin resistance [5, 6]. Recently, the triglyceride-glucose (TyG) index has been used to measure insulin resistance. The triglyceride-glucose index is derived from blood levels of fasting glucose and triglycerides. It is calculated
by taking the natural logarithm of half of the product of glucose and triglyceride levels. High availability and easy measurement make this index very useful in clinical practice. Regardless of glucose tolerance or obesity, the TyG index inversely correlated with insulin resistance and validated against the gold standard euglycemic-hyperinsulinemic clamp test [7]. As a good marker of insulin resistance, the TyG index is associated with an increased risk of diabetes mellitus [8], stroke [9], coronary artery disease [10, 11] in healthy individuals. It is beneficial for estimating the risk of adverse prognosis of symptomatic and asymptomatic coronary artery disease and acute myocardial infarction [12-14]. In addition, there is evidence that the TyG index is also correlated with asymptomatic carotid artery atherosclerosis [15]. We aimed to examine the relationship between the TyG index and the intima-media thickness (IMT) of the thoracic aorta in patients who underwent transesophageal echocardiography for suspected structural heart disease such as atrioventricular septal defect, patent foramen ovale, and valvular heart diseases.

**Methods**

**Study population**

One hundred twenty-two patients who had undergone transesophageal echocardiography between January 2021 and June 2021 for suspected structural heart disease such as atrial septal defect, ventricular septal defect, and thrombus in the left atrial appendage were enrolled in the study. Patients with hypertension, diabetes mellitus, coronary artery disease, peripheral artery disease, stroke, chronic renal failure (eGFR< 30ml/min) were excluded from the study. Patients taking statins, fibrates, ezetimibe, PCSK9 inhibitors, antidiabetics, steroids, and other drugs that impact lipid characteristics or insulin sensitivity were also excluded from the study. Blood samples were drawn after 12 hours of fasting before the transesophageal echocardiography procedure. Triglyceride-glucose index was calculated using the formula; $\text{TyG} = \ln \left( \frac{\text{Glucose} \text{ (mg/dl)} \times \text{Triglycerides} \text{ (mg/dl)}}{2} \right)$. Major risk factors for cardiovascular disease were recorded for each participant. The local ethics committee approved the study design. All participants carefully read and approved the informed consent. The study was conducted according to the Helsinki Declaration.

**Statistics**

SPSS 22.0 software (SPSS Inc. Chicago, IL) was used for statistical analysis. The Shapiro-Wilk test was used to analyze the normality of continuous variables. Continuous variables with a normal distribution were expressed as the mean, standard deviation, while non-normally distributed variables were expressed as the median (minimum-maximum). Student's t-test and Mann-Whitney U tests compared normally and non-normally distributed continuous variables between two groups. For bivariate analysis, Pearson and Spearman correlation coefficients were reported. Binary logistic regression analysis was used to determine the variables independently associated with IMT. All variables known to play a role in atherosclerosis were entered into the regression model regardless of the bivariate analysis results. A p-value less than 0.05 was considered statistically significant.

**Transthoracic and transesophageal echocardiography**
Transthoracic echocardiography and transesophageal echocardiography were performed using a commercially available system (Vivid 7R, GE Medical Systems, Horten, Norway). The modified Simpson's approach was used to calculate the left ventricular ejection fraction [16]. Following a 12-hour fasting interval, all patients underwent transesophageal echocardiography with a 5Mhz multiplane transesophageal transducer. After oropharyngeal anesthesia with lidocaine spray, subjects were put in left decubitus with the left arm under their heads. The transducer was inserted through the mouth into the esophagus and gastric cavity to observe the cardiac and aortic structures. transesophageal echocardiography was performed by an expert cardiologist who was blinded to other laboratory tests. All patients tolerated transesophageal echocardiography well, and there were no complications. An expert observer independently interpreted all the recorded images. The thoracic aortic IMT was defined as the distance from the leading edge of the lumen-intima interface to the leading edge of the media–adventitia interface of the far wall. Intima-media thickness was measured manually in the thoracic aorta in six segments: ascending aorta, arcus aorta, from distal arch to abdominal aorta was separated into four independent portions, each 5 cm long. The highest value for the IMT among the six segments was recorded [17].

**Results**

The study population is composed of 122 patients (mean age 40.39 ± 15.29, 65 females (53.27%)). The study population was divided into two groups according to their median IMT. The first group was composed of 61 subjects (mean age 33.25 ± 11.07 years, 33 females (50.8%)) with IMT equal or less than the median value of 1.42 mm; the second group was composed of 61 subjects (mean age 47.52 ± 15.67 years, 32 females (49.2%)) greater than the median IMT. Atrial septal defect (39 (63.9%) vs. 39 (63.9%), p= 1), atrial fibrillation (16 (26.2%) vs. 15 (24.6%), p = 0.942) and valvular heart disease (6 (9.8%) vs. 7 (11.5%), p= 0.894) were the indications of transesophageal echocardiography (Table 1).

Age, creatinine, glucose, triglyceride, and TyG index were higher in the high IMT group. Gender, smoking status, cholesterol levels, and transesophageal echocardiography indications were similar among the groups (Table 1).

The IMT was correlated with age, glucose, triglycerides, creatinine, and TyG index. There was no correlation between cholesterol levels and IMT (Table 2).

Binary logistic regression analysis was performed to predict the variables associated with having high intima media thickness. In binary logistic regression analysis TyG index was positively related with IMT (β=1.726, exp(B) = 5.621 95%CI = 1.139 – 27.728, p = 0.034). In addition, age was related with IMT (β= 0.091, exp(B)= 1.095 95%CI = 1.041- 1.152, p<0.001) (Table 3).

**Discussion**
We showed that the TyG index is independently related to aortic IMT, a marker of subclinical atherosclerosis in healthy individuals without any previous cardiovascular disease or diabetes. Several investigations have linked the TyG index to atherosclerotic cardiovascular disease risk factors such as type 2 diabetes [8], hypertension [18], and metabolic syndrome [19]. Other cardiovascular disease surrogate measures related to the TyG index include coronary artery calcium score [20], IMT of carotid arteries, and arterial stiffness [21, 22]. A few studies have found a link between the TyG index and cardiovascular disease in high-risk patients with diabetes and chronic renal disease [23-25]. To our knowledge, our study is the first to show an independent relationship between the TyG index and the thoracic aorta IMT. The Triglyceride-glucose index is directly proportional to the blood glucose and triglyceride levels, and both levels appear to be increased in individuals with insulin resistance. The causal relationship between insulin resistance and atherosclerosis is well established in the literature.

Examining the association between blood glucose and triglyceride levels separately with atherosclerosis can reveal the relationship between the TyG index and atherosclerosis. At the beginning of insulin resistance, increased lipolysis of stored triglycerides in adipose tissue and increased production of fatty acids in the liver increase triglyceride levels before elevating plasma glucose levels. Therefore, at the beginning of insulin resistance, fasting glucose remains in the normoglycemic range [26]. Several meta-analyses with many patients have shown that fasting plasma glucose levels, already within the normoglycemic range (<100 mg/dL), are associated with the risk of developing coronary heart disease in subjects without diabetes mellitus. The risk of coronary disease increased linearly with blood glucose levels, independent of other established cardiovascular disease risk factors. The increased risk of diabetes [27] did not mediate it. Fasting glucose concentration is associated with coronary artery risk in people without diabetes, with an increased risk of 6% for every 1 mmol/L increment (18 mg/dL) in fasting plasma glucose, according to a meta-analysis of 26 prospective studies involving over 300,000 people [28].

Another finding in insulin resistance is elevated triglyceride levels, whose relationship with cardiovascular risk and mortality is disputed [29]. The difficulty in isolating hypertriglyceridemia's effect on cardiovascular disease is that it is frequently associated with other atherogenic lipid diseases, such as decreased HDL cholesterol and higher LDL cholesterol levels. In our study, we entered all lipid parameters in multivariate analysis to isolate the effect of triglycerides on IMT. However, in some studies, the relationship between triglyceride levels and cardiovascular disease became nonsignificant after adjusting for other lipid disorders and major variables; most studies found a direct association of triglyceride levels with increased risk and worse outcomes. Elevation of plasma free fatty acids activates the proinflammatory nuclear factor kappa-light-chain-enhancer of activated B cells pathway [30], resulting in increased hepatic expression of several proinflammatory cytokines, including TNF-α, IL1-β, IL6, matrix metalloproteinases [31], these inflammatory changes which play a significant role in the development of atherosclerosis [32]. It has been shown that daily administration of 2 g of icosapent ethyl reduces the frequency of cardiovascular death and ischemic events in patients who have recently used statins for coronary artery disease and still have high triglyceride levels (135-499 mg/dl).
Since plaque thickness rather than morphology is thought to be a more objective and reliable indicator of atherosclerotic disease, most grading systems use the maximum plaque thickness of the most diseased segment. However, there are a few grading systems of aortic atheroma based on IMT; no standard or widely accepted IMT cut-off is available for classification [17]. We used the median value of 1.42 mm as a cut-off to indicate high IMT. In literature, IMT higher than 1.5 mm was associated with an increased risk of coronary artery disease and stroke [33]. Although our definition of having a high IMT may seem arbitrary, the median IMT value of the patients in our study is very close to the value known to increase the risk of coronary artery disease and stroke (1.42 vs. 1.5), provides a rational basis for our definition. Since atherosclerosis begins in the thoracic aorta earlier than in the carotid arteries, our study has the advantage of delineating the relationship between TyG and subclinical atherosclerosis better than studies performed on the carotid arteries.

Lifestyle modifications or drug therapies are recommended for primary prevention by calculating the fatal and non-fatal cardiovascular disease risk using scoring systems (SCORE2 and SCORE2-OP) based on age, gender, blood pressure, smoking status, and non-HDL cholesterol levels [3]. In addition, some non-invasive tests like coronary artery calcium score [34, 35], carotid ultrasound helps to reclassify individuals to a higher or lower risk category. Based on our findings, we may suggest that the TyG index can also be used for adding information on the calculated SCORE risk.

Most of the subjects included in our study are young individuals (mean age 40.38 ± 15.29 years) with low cardiovascular risk. They represent a narrow area of the cardiovascular risk spectrum compared to the general population. In addition, the cross-sectional structure of our study makes it difficult to reveal the cause-effect relationship. These are major limitations of our study.

**Conclusion**

We showed that the TyG index predicts having a higher IMT independently from other major risk factors for atherosclerosis in healthy subjects without any cardiovascular disease. Based on this finding, the TyG index may be a useful marker to identify individuals at high risk of developing cardiovascular diseases.

**Abbreviations**

IMT: intima media thickness, TyG: triglyceride glucose.

**Declarations**

We declare we have no position in a healthcare-related company, do not hold patents, receive any funding or payment from external sources, and disclose no conflicts of interest.

**Ethics approval and consent to participate**
The study was conducted in accordance with the declaration of Helsinki, local regulations, and the International Conference on Harmonization Good Clinical Practice guidelines. The local ethics committee of University of Health Sciences, Adana City Training and Research Hospital approved the study design, amendments and informed consent form on 2nd October 2021 (meeting no: 87, issue no: 1538). All subjects gave their informed consent.

Consent for publication
Written informed consent for publication was obtained from all participants

Availability of data and materials
The dataset supporting the results of this article is available from the corresponding author upon request.

Competing Interest
The authors declare that they have no competing interests.

Funding
No.

Authors’ contributions
SÖ and GY made substantial contributions to study design and concept. ÖDU was responsible for data collection. SÖ did the data analysis and wrote the manuscript. GY revised the manuscript. All authors have full access to all the data in the study and take responsibility for the integrity and security of the data. All authors read and approved the final manuscript.

Acknowledgments
We declare we have no position in a healthcare-related company, do not hold patents, receive any funding or payment from external sources, and disclose no conflicts of interest.

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### Table 1. Comparison of IMT groups

<table>
<thead>
<tr>
<th></th>
<th>IMT low group n=61</th>
<th>IMT high group n=61</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>33.25 ± 11.07</td>
<td>47.52 ± 15.67</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender (female), n (%)</td>
<td>33 (50.8%)</td>
<td>32 (49.2%)</td>
<td>1</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>14 (23%)</td>
<td>13 (21.3%)</td>
<td>1</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>122.42 ± 11.44</td>
<td>123.56 ± 10.98</td>
<td>0.572</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>81.34 ± 8.67</td>
<td>82.42 ± 7.92</td>
<td>0.474</td>
</tr>
<tr>
<td>Waist to hip ratio</td>
<td>0.92 ± 0.09</td>
<td>0.9 ± 0.09</td>
<td>0.22</td>
</tr>
<tr>
<td>Body mass index, kg/m^2</td>
<td>26.1 ± 3.12</td>
<td>25.88 ± 3.48</td>
<td>0.713</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>62.65 ± 3.51</td>
<td>62.62 ± 3.98</td>
<td>0.969</td>
</tr>
<tr>
<td>Hemoglobin, (gr/dl)</td>
<td>13.88 ± 2.88</td>
<td>13.8 ± 1.82</td>
<td>0.077</td>
</tr>
<tr>
<td>BUN</td>
<td>24.1 ± 7.03</td>
<td>27.64 ± 10.73</td>
<td>0.068</td>
</tr>
<tr>
<td>Creatinin, (mg/dl)</td>
<td>0.74 ± 0.15</td>
<td>0.8 ± 0.2</td>
<td>0.042</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>87.73 ± 11.1</td>
<td>98.45 ± 25.41</td>
<td>0.004</td>
</tr>
<tr>
<td>Total Cholesterol, (mg/dl)</td>
<td>175 ± 38.97</td>
<td>185.36 ± 42.4</td>
<td>0.169</td>
</tr>
<tr>
<td>LDL-Cholesterol, (mg/dl)</td>
<td>109.02 ± 33.62</td>
<td>117.84 ± 34.21</td>
<td>0.159</td>
</tr>
<tr>
<td>HDL-Cholesterol, (mg/dl)</td>
<td>46.6 ± 13.17</td>
<td>43.37 ± 10.34</td>
<td>0.141</td>
</tr>
<tr>
<td>Triglycerides, (mg/dl)</td>
<td>91 (28-329)</td>
<td>113 (29.3-397)</td>
<td>0.006</td>
</tr>
<tr>
<td>Triglyceride-Glucose Index</td>
<td>8.37 ± 0.53</td>
<td>8.69 ± 0.59</td>
<td>0.003</td>
</tr>
</tbody>
</table>

**Indication of TEE**

<table>
<thead>
<tr>
<th></th>
<th>IMT low group n=61</th>
<th>IMT high group n=61</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial septal defect, n, %</td>
<td>39 (63.9%)</td>
<td>39 (63.9%)</td>
<td>0.947</td>
</tr>
<tr>
<td>Atrial fibrillation, n, %</td>
<td>16 (26.2%)</td>
<td>15 (24.6%)</td>
<td>0.947</td>
</tr>
<tr>
<td>Valvular disease, n, %</td>
<td>6 (9.8%)</td>
<td>7 (11.5%)</td>
<td>0.894</td>
</tr>
</tbody>
</table>

BP: Blood pressure, IMT: Intima-media thickness, TEE: Transesophageal echocardiography. Students t-test and Kruskal Wallis tests were used.

### Table 2. Correlations of Intima-media thickness
Table 3. Binary logistic regression analysis for having high Intima-media thickness.

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>Exp(B)</th>
<th>95% CI for EXP(B)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.091</td>
<td>1.095</td>
<td>1.041 - 1.152</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender</td>
<td>0.097</td>
<td>1.102</td>
<td>0.378 - 3.216</td>
<td>0.859</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.483</td>
<td>1.621</td>
<td>0.52 - 5.057</td>
<td>0.405</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>-0.02</td>
<td>0.98</td>
<td>0.925 - 1.039</td>
<td>0.504</td>
</tr>
<tr>
<td>HDL-Cholesterol</td>
<td>0.007</td>
<td>1.007</td>
<td>0.938 - 1.081</td>
<td>0.843</td>
</tr>
<tr>
<td>LDL-Cholesterol</td>
<td>-0.001</td>
<td>0.999</td>
<td>0.942 - 1.061</td>
<td>0.985</td>
</tr>
<tr>
<td>Triglyceride Glucose Index</td>
<td>1.726</td>
<td>5.621</td>
<td>1.139 - 27.728</td>
<td>0.034</td>
</tr>
</tbody>
</table>

Nagelkerke $R^2$ = 0.289. Binary logistic regression analysis was used.