

# Evaluation of the relationship between mitral annular calcification and triglyceride-glucose index

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## ABSTRACT

**Aims:** Mitral annular calcification (MAC) is an echocardiographic condition with a multicomponent etiopathogenesis, one of which is insulin resistance. Triglyceride-glucose (TyG) index is an excellent biochemical parameter that has proven itself in determining insulin resistance in recent years. This study aims to reveal the relationship between the TyG index and the presence of MAC.

**Methods:** The study included 159 patients with MAC and 167 control group. The control group has similar demographic characteristics such as age, gender, presence of hypertension (HT), and diabetes mellitus with the MAC group. TyG index was calculated as a formula:  $\ln[\text{fasting triglyceride (mg/dl)} \times \text{fasting plasma glucose (mg/dl)} / 2]$ .

**Results:** The mean age of the patients was 74.2 and 48.2% of the patients were male. Coronary artery disease (CAD) ( $p: 0.031$ ), glucose ( $p: 0.001$ ), total cholesterol ( $p: 0.009$ ), low-density lipoprotein (LDL) ( $p: 0.004$ ), triglyceride (TG) ( $p < 0.001$ ) levels and TyG index ( $p < 0.001$ ) were higher in MAC group. In the multivariate regression analysis, TG ( $p: 0.004$ ) and TyG index ( $p < 0.001$ ) were found to be independent risk factors. As a result of the ROC analysis, the cut-off value for estimating MAC was found to be 8.81 [(sensitivity: 77.3%, specificity: 76.5%, AUC (95% CI) 0.756 (0.704-0.807)  $p < 0.001$ )].

**Conclusion:** In this study, a high TyG index was found to be an independent risk factor for MAC. The TyG index was found to be a better biomarker than TG and glucose alone in predicting MAC. Further extensive studies are necessary to determine the importance and use of TyG in MAC.

**Keywords:** Mitral annular calcification, insulin resistance, triglyceride-glucose index

## INTRODUCTION

Mitral annular calcification (MAC) is defined as not only a local, chronic and degenerative process characterized by the precipitation of calcium and phosphate in the fibrous tissue of the mitral ring but also as an active and regulated molecular process related to lipid and mineral metabolism, hemodynamic stress and inflammation.<sup>1,2</sup> The mitral annulus is one of the most common sites of calcification after the coronary arteries.<sup>3</sup> Although its name suggests that calcification is limited to the mitral annulus only, it has been observed in surgical specimens that calcification may also extend to the chordae tendineae, papillary muscles, and left ventricle.<sup>4</sup> Major risk factors for the development of MAC are age, female gender, obesity, hypertension (HT), diabetes mellitus (DM), dyslipidemia, chronic kidney disease and smoking.<sup>5,6</sup>

The most common radiographic method for the diagnosis of MAC is echocardiography. MAC appears as an irregular

and echo-dense structure, and its size increases with the severity of calcification.<sup>7</sup> The most specific diagnostic test is computed tomography.<sup>7,8</sup> Although it varies depending on the imaging method and the population, the prevalence of MAC varies between 5% and 47%.<sup>1,9</sup>

In clinical practice, MAC is associated with not only mitral valve dysfunction which causes systemic diseases but also cardiovascular diseases.<sup>2</sup> MAC, which is associated with atherosclerosis, heart failure, stroke, and atrial fibrillation, has also been independently associated with all-cause and cardiovascular mortality.<sup>10-12</sup> This strong link encouraged researchers to design studies by emphasizing MAC's pathophysiology and clinical value.

Despite its importance in cardiovascular pathologies, the mechanism of MAC formation still needs to be fully understood. Previous data have shown that inflammation, oxidative stress, dyslipidemia, and dysregulation in bone mineral metabolism are

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essential in developing MAC in pathogenesis.<sup>2,13,14</sup> In addition to all these processes, it is known that insulin resistance also plays a role in the mechanism of MAC formation, such as coronary calcification.<sup>15</sup> However, it is unclear whether insulin resistance affects calcification formation beyond metabolic syndrome components and cardiovascular risk factors.<sup>16</sup> However, measuring insulin resistance requires complex techniques, a more straightforward method, the Hemostasis Model Evaluation (HOMA), is routinely used. On the other hand HOMA is a relatively expensive method requiring glucose and insulin measurement. In recent years, the triglyceride-glucose (TyG) index, based on fasting glucose and triglyceride (TG) measurements, has been a reliable marker with high sensitivity in the assessment of insulin resistance.<sup>17</sup> The relationship of the TyG index with coronary and peripheral arterial diseases, stroke, and HT has been demonstrated.<sup>18-20</sup> Until now, there is not enough data about the importance of the TyG index in estimating MAC in the literature.

This study aims to evaluate the importance of the TyG index as a screening parameter of the early diagnosis of MAC by examining the relationship between the TyG index, which has proven to be a good biochemical parameter in demonstrating insulin resistance, and MAC.

## METHODS

The study was initiated with the approval of the Ankara City Hospital No: 1 Clinical Researches Ethics Committee (Date: 19/07/2023, Decision No: AEŞH-EK1-2023-273). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

### Study Population

This single-center study retrospectively scanned the files of adult patients who underwent echocardiography between January 2019 and June 2023. A study group with 159 patients with MAC and a control group with 167 patients with similar demographic characteristics such as age, gender, DM and HT were included. The participants' demographic, laboratory and echocardiographic data were recorded from the hospital system.

Patients with rheumatic heart valve disease, prosthetic heart valve disease, acute and chronic inflammatory disease, advanced renal failure (stage 4-5), liver failure, active malignancy, disease related to calcium metabolism, and patients receiving steroid therapy for any reason were excluded.

### Laboratory & Imaging Data

Laboratory parameters, including triglyceride and glucose were recorded from the hospital records. Blood

samples were taken from the patients by venous route after 8 hours of fasting. TyG index was calculated as  $\ln(\text{fasting triglyceride} \times \text{fasting glucose}/2)$ .<sup>21</sup>

Transthoracic echocardiography was performed by the same cardiologist with the Philips Healthcare iE33 xMATRIX echocardiography (Philips Medical Systems, MA, USA) device with an S5-1 transducer. MAC; parasternal long or short axis was defined as a dense echocardiographic structure with localized reflective features at the junction of the atrioventricular groove and the anterior or posterior leaflet of the mitral valve on apical two- or four-chamber views.<sup>22</sup>

### Statistical Analysis

Continuous variables are mean  $\pm$  standard deviation, and categorical data are shared percentages and numbers (n). Student's t-test was used for normally distributed data, and the Mann-Whitney U test was used for non-normally distributed data. Categorical data were compared with the chi-square test. Univariate regression analysis was performed to find predictive factors for developing MAC. Multivariate regression analysis was applied to the parameters that were significant in the univariate test and independent risk factors for MAC development were determined. Receiver operating characteristic (ROC) analysis was used to estimate the optimum cut-off value of the TyG Index to indicate MAC. Sensitivity, specificity, and area under the curve (AUC) were calculated. Two-sided  $p < 0.05$  was considered significant. Data were analyzed with the SPSS 23.0 statistical program (SPSS Inc., NY, USA).

## RESULTS

48.2% (n=157) of the patients were male. The mean age of the patients was 71.4 years. There was no difference between age, gender, HT, DM, smoking and EF. Only coronary artery disease (CAD) was higher in patients with MAC (n=79 (49.7%) vs. n=65 (38.9%),  $p = 0.031$ ). No difference was found between hemoglobin, WBC, platelet, creatinine and high-density lipoprotein (HDL). In MAC patients, glucose ( $p < 0.001$ ), total cholesterol ( $p = 0.009$ ), Low-density lipoprotein (LDL) ( $p = 0.004$ ), TG ( $p < 0.001$ ) and TyG index ( $8.90 \pm 0.44$  vs.  $8.43 \pm 0.49$ ,  $p < 0.001$ ) were higher than control group ([Table 1](#)).

As a result of univariate regression analysis performed to determine the variables predicting the development of MAC, glucose ( $p = < 0.001$ ), total cholesterol ( $p = 0.010$ ), TG ( $p = < 0.001$ ) and TyG index ( $p = 0.001$ ) were found to be predictive factors for the development of MAC. As a result of multivariate regression analysis, TG ( $p = 0.004$ ) and TyG index ( $p = < 0.001$ ) were found to be independent risk factors ([Table 2](#)).

**Table 1.** Basal demographic and laboratory characteristics of the patients and control group.

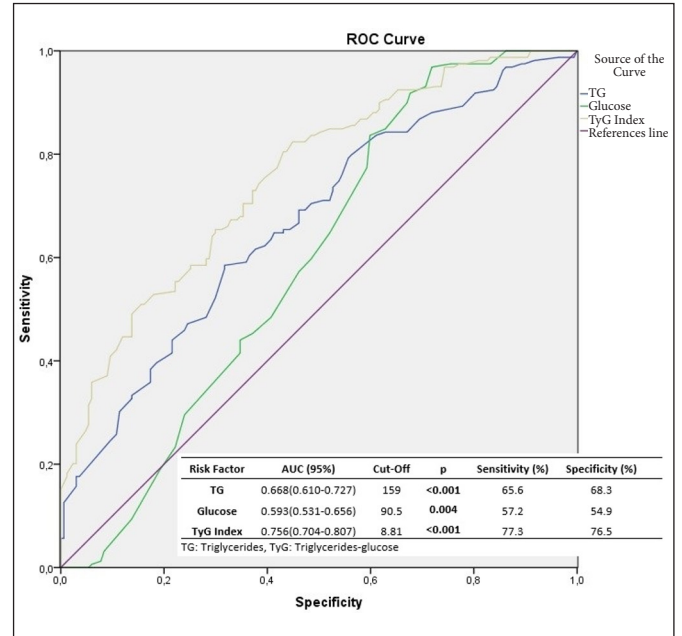
	MAC (n=159)	Control group (n=167)	P
Age, years	71.9 ±6.8	70.8±6.5	0.134
Male, n (%)	72 (45.3)	85 (50.9)	0.183
HT, n (%)	50 (31.4)	46 (27.5)	0.258
DM, n (%)	66 (41.5)	74 (44.3)	0.354
CAD, n (%)	79 (49.7)	65 (38.9)	0.031
Smoking, n (%)	50 (31.4)	46 (27.5)	0.258
EF, %	62.4±11.2	63.1±10.8	0.376
Hemoglobin, g/dl	12.7±2.4	12.9±2.6	0.481
WBC, 10 <sup>3</sup> /mm <sup>3</sup>	7.8±1.9	7.7±2.4	0.205
Platelet, 10 <sup>3</sup> /mm <sup>3</sup>	276.3±75.5	279.6±54.7	0.662
Glucose, mg/dl	91.5±5.8	87.7±8.9	<0.001
Creatinin, mg/dl	1.17±0.28	1.16±0.32	0.728
Total cholesterol, mg/dl	207.2±38.7	196.4±38.2	0.009
LDL, mg/dl	126.3±31.9	121.4±33.8	0.004
HDL, mg/dl	50.5±6.6	51.9±5.8	0.236
TG, mg/dl	168.3±63.5	131.2±49.4	<0.001
TyG Index	8.90±0.44	8.43±0.49	<0.001

MAC: Mitral annular calcification, HT: Hypertension, DM: Diabetes mellitus, CAD: Coronary artery disease, EF: Ejection fraction, WBC: White blood cell, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, TG: Triglycerides, TyG: Triglycerides-Glucose

The ROC analysis performed to determine the optimal cutoff values of the TG, glucose and TyG index parameters in predicting the MAC development revealed the optimal cut-off values for TG, glucose and TyG index as 159 [sensitivity: 65.6%, specificity: 68.6%, AUC (95% Confidence Interval (CI)) 0.668 (0.610-0.727) p<0.001], 90.5 ((sensitivity: 57.2%, specificity: 54.9%, AUC (95% CI) 0.593(0.531-0.656) p:0.004), and 8.81 ((sensitivity: 77.3%, specificity: 76.5%, AUC (95% CI) 0.756 (0.704-0.807) p<0.001), respectively (Figure 1).

**DISCUSSION**

In this study, the relationship between MAC and TyG index was evaluated. It was observed that there was a significant relationship between the triglyceride-glucose index and MAC. In multiple regression analysis, high TG and TyG index levels were found to be an independent risk factor in predicting MAC formation. In addition, MAC was more common in patients with CAD and high glucose, LDL and total cholesterol levels. This study is important as it is the



**Figure 1.** Receiver operating characteristic analysis results for TG, glucose, and TyG Index.

first study to evaluate the relationship between MAC and the TyG index, as far as we know.

Mitral annular calcification is an echocardiographic finding that clinically focuses primarily on the degree of accompanying valve dysfunction. It has been proven to be strongly associated with cardiovascular morbidity and mortality in recent years.<sup>23</sup> It is frequently seen in the elder age, as in many other MAC studies; the elderly population was found to be the majority in our study.<sup>5,6</sup> The biological mechanisms explaining the relationship of MAC with cardiovascular diseases have not yet to be fully elucidated. However, it is known that the histopathology of MAC is similar to coronary atherosclerosis. These two diseases share cardiovascular risk factors (HT, DM, dyslipidemia, smoking, etc.) and common pathophysiological mechanisms.<sup>23-25</sup> However, contrary to the atherosclerosis paradigm, MAC is more common in women. In our study, the female sex ratio was predominant in the MAC group, similar to previous clinical studies.<sup>25,26</sup> In addition, the rate of CAD was higher in patients with MAC in our study. This result supported previous studies.<sup>9</sup>

**Table 2.** Predictors of mitral annular calcification.

	Univariate analysis OR (95% CI)	P	Multivariate analysis OR (95% CI)	P
CAD	1.550(0.998-2.406)	0.510	**	**
Glucose	1.051(1.025-1.076)	<0.001	0.999(0.992-1.006)	0.706
Total cholesterol	1.008(1.002-1.014)	0.010	0.999(0.992-1.006)	0.784
LDL	1.002(0.989-1.005)	0.181	**	**
TG	1.012(1.007-1.016)	<0.001	1.016(1.005-1.027)	0.004
TyG Index	1.126(1.072-1.219)	<0.001	1.088(1.012-1.195)	<0.001

CAD: Coronary artery disease, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, TG: Triglycerides, TyG: Triglycerides-Glucose



Although the physiopathogenesis of mitral annular calcification is not clear, it is known to occur due to multifactorial mechanisms such as dyslipidemia, inflammation, oxidative stress, bone mineral metabolism disorders and insulin resistance.<sup>2,14</sup> Previous studies revealed results proving the relationship between inflammation and MAC, one of these mechanisms.<sup>3,6,26</sup> The relationship between insulin resistance and MAC has been relatively less studied. Recently, Grigorescu et al.<sup>6</sup> showed that patients with MAC have higher insulin resistance with higher HOMA C-peptide and C-peptide index. On the other hand, Tison et al.<sup>16</sup> showed a positive and graded relationship between insulin resistance and extra-coronary calcification, including in patients with MAC, based on HOMA level. In our study, we tried to prove the existing relationship by using the non-insulin level-based TyG index, which was obtained simply as an indicator of insulin resistance. At the same time, the relationship between the development of MAC, which is a multi-component process, and inflammation is known, and studies have revealed that systemic inflammation is more common in patients with insulin resistance.<sup>6</sup> Our results suggest that the higher detection of MAC in patients with high TyG index may be both a result and a cause. Thus, there may be a bidirectional relationship between the TyG index MAC and systemic inflammation.

The TyG index used in our study was first studied as an insulin resistance marker candidate and proved to be a good biochemical parameter in demonstrating insulin resistance.<sup>17,27</sup> Today, this index has not been used routinely due to the lack of studies that will improve its capacity and standardize it in detecting insulin resistance. However, the fact that it is a cheaper and more accessible parameter than insulin level-based methods that show insulin resistance has created an advantage in using this index in various epidemiological and clinical studies.<sup>28</sup> In recent studies, TyG is associated with cardiovascular diseases such as coronary artery disease, peripheral vascular disease, stroke, HT, the risk of developing type 2 DM and metabolic syndrome.<sup>18,19</sup> Although the detailed mechanism of the relationship between cardiovascular diseases and the TyG index has not been fully demonstrated, the TyG index has been accepted as a valuable indicator associated with insulin resistance and cardiovascular disease.<sup>20</sup> We also determined a positive relationship with MAC, whose relationship was not examined before. Although the exact reason for this relationship is unclear due to the nature of the study design.

In ROC analysis, the TyG index predicts MAC; obtained better results than the TG and glucose parameters it contains alone. The sensitivity and specificity values of the TyG index were higher than glucose and TG. This suggests that the TyG index is a more reliable and helpful biomarker.

## Limitations

Our study has several limitations. The most important limitation of the study is that it is a single-center and retrospective study. This situation needs to make it possible to explain the causality of the relationship between MAC and the TyG index. Secondly, a selection bias is possible when initially forming the control group. The results should be interpreted with caution and further scrutinized in larger multicenter studies. Finally, since our study is retrospective, there is no data or classification regarding the severity of MAC.

## CONCLUSION

This study showed a significant positive correlation between MAC and the TyG index, which can be calculated in routine blood parameters. A higher TyG index independently predicted a higher rate of MAC. Patients with a high TyG index can be observed more closely regarding MAC formation in clinical practice. In this group, index-reducing treatments may slow down the occurrence of MAC. However, multicenter, randomized, prospective studies are needed to support and clarify these hypotheses.

## ETHICAL DECLARATIONS

**Ethics Committee Approval:** The study was initiated with the approval of the Ankara City Hospital No:1 Clinical Researches Ethics Committee (Date: 19.07.2023, Decision No: AEŞH-EK1-2023-273).

**Informed consent:** Because the study was designed retrospectively, no written informed consent form was obtained from patients.

**Referee Evaluation Process:** Externally peer reviewed.

**Conflict of Interest Statement:** The authors have no conflicts of interest to declare.

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**Author Contributions:** All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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