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The impact of gender differences on the roles of the atherogenic index of plasma and triglyceride-glucose index in predicting moderate to severe coronary artery calcification

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ABSTRACT

Objectives: This study aimed to evaluate the association of the triglyceride-glucose (TyG) index and the atherogenic index of plasma (AIP) with moderate-to-severe coronary artery calcium score (CACS), with a particular focus on gender differences. Given the gender-specific variations in the development of coronary artery calcification, tailored diagnostic approaches are required.

Methods: In this retrospective, single-center study, 246 consecutive patients aged 25-77 years who underwent 128-slice coronary computed tomography angiography (CCTA) for coronary artery disease screening between June 2024 and January 2025 were analyzed. Patients were categorized into three groups according to their CACS: Group 1 (CACS=0), Group 2 (CACS=1-99), and Group 3 (CACS≥100). Demographic characteristics and medical histories were recorded. Biochemical parameters, lipid panel, and hemogram values were analyzed from venous blood samples collected after 12 hours of fasting. Multivariate logistic regression analyses were performed to identify independent predictors of moderate-to-severe CACS in both genders.

Results: In women, advanced age (odds ratio [OR]=1.126; 95% confidence interval [CI]: 1.031–1.136; P<0.001), elevated triglyceride levels (OR=0.964; 95%CI:0.937–0.992; P=0.011), and a higher TyG index (OR=35.317;95%CI:6.328–187.356; P=0.002) were independently associated with moderate-to-severe CACS. In men, advanced age (OR=1.083; 95% CI:1.007–1.165; P=0.032), severe coronary artery stenosis (OR=12.298; 95% CI: 1.451–104.208; P=0.021), and smoking (OR=8.771; 95%CI: 1.810-42.501; P=0.007) were independent predictors. AIP was not identified as an independent predictor of moderate-to-severe CACS in either gender.

Conclusions: Advanced age was independently associated with CACS in both genders. The TyG index was a significant predictor of moderate-to-severe CACS in women, while traditional risk factors, such as smoking and severe coronary artery stenosis, were more relevant in men. AIP was not an independent predictor of moderate-to-severe CACS in either gender.

Keywords: Coronary artery calcium score, gender differences, atherosclerosis, atherogenic index of plasma, triglyceride-glucose index

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Coronary artery calcium scoring (CACS), assessed by coronary computed tomography angiography (CCTA), is a well-established, noninvasive marker of coronary atherosclerosis and an independent predictor of major adverse cardiovascular events (MACE) [1, 2]. Several metabolic and inflammatory conditions, including hyperlipidemia, diabetes mellitus (DM), and systemic inflammation, contribute to the progression of coronary artery calcification (CAC) [3]. Notably, gender differences influence both the prevalence and characteristics of CAC; men tend to develop calcified plaques at younger ages, whereas non-calcified or mixed plaques are more common in premenopausal women. After menopause, the prevalence of CAC in women increases significantly [4-6].

Considering the gender-specific differences in the development of CAC, it is essential to incorporate these variations when designing effective diagnostic methods for CAD [7]. In recent years, two metabolic markers - the triglyceride-glucose (TyG) index and the atherogenic index of plasma (AIP) - have emerged as potential predictors of subclinical atherosclerosis. The TyG index is a validated surrogate for insulin resistance, while AIP reflects atherogenic lipid imbalance [8]. Both have been associated with coronary artery disease (CAD) and CAC independent of traditional risk factors, including DM [9, 10]. However, few studies have evaluated whether the predictive performance of these indices differs by gender, despite the known sex-specific pathophysiology of atherosclerosis.

Understanding the gender-specific predictive value of TyG and AIP may help refine cardiovascular risk stratification, especially in women, who often receive less aggressive diagnostic and preventive care. Therefore, this study aimed to investigate the association of the TyG index and AIP with moderate-to-severe CACS, with particular emphasis on sex-related differences in predictive value.

METHODS

Study Design

The research was carried out on 246 consecutive patients in the age range of 25-77 years admitted to the cardiology outpatient clinic of Siirt Training and Research Hospital and underwent 128-slice CCTA for CAD screening between June 2024 and January 2025, retrospectively. Patients with severe renal failure, liver failure, thyroid dysfunction, structural heart disease, infection, autoimmune disease, malignancy, patients for whom effective CCTA cannot be performed due to arrhythmia, pregnant women and breastfeeding women, patients with previously known CAD and those who have undergone interventional cardiovascular procedures, patients using fenofibrate due to hypertriglyceridemia and patients taking statins were not included in the study. Patients with a CACS of 0 were defined as the control group (Group 1). Patients with a CACS between 1 and 99 were defined mild CACS group as Group 2, and patients with a CACS≥100 were defined moderate to severe CACS group as Group 3.

The research adhered to the norms of the Declaration of Helsinki and was granted approval by Siirt University Noninterventional Clinical Research Ethical Committee (Date: 28.11.2024, Decision No: 2024/12/01/04).

Demographic Findings, Laboratory Analyzes, the CCTA and CACS Analysis

The patients' age, gender, systolic and diastolic tension (TA) measurements, body mass index (BMI), previous medical history (HT, DM, HL history), cardiac family history and smoking habits were recorded. Biochemical parameters such as fasting blood sugar (FBG), uric acid, C-reactive protein (CRP), and hemoglobin A1c (HbA1c) values were measured in venous blood samples taken after 12 hours of fasting. For lipid parameters, total cholesterol, triglyceride, LDL, and high-density lipoprotein (HDL) values were obtained using the Beckman Coulter device and kits. Then, the TyG index was calculated using the natural logarithm (ln) formula (fasting triglyceride × fasting glucose/2). Atherogenic index of plasma (AIP) was obtained by taking the logarithm of the ratio of serum triglyceride level to high-density lipoprotein level. LDL/HDL, total cholesterol/HDL parameters were calculated. Additionally, neutrophil, lymphocyte, and monocyte were assessed using the Mindray device and kits. Neutrophile/lymphocyte ratio (NLR) and monocyte-HDL ratio values were calculated.

5 mg intravenous metoprolol was administered within 2 to 30 minutes before the procedure to patients who had a heart rate of 65/min before the procedure

and had no contraindication to beta blocker treatment. CACS was measured with a 128-slice General Electric CT scanner device using the prospective electrocardiogram (ECG) gating method with non-contrast 120 KV, 300 mAs values, 3 mm slice thickness, without any overlap or gap. CAC data collection was performed prospectively synchronized with the patient's ECG by gating in high pitch mode by operating it in the craniocaudal direction during breath holding in mid-inspiration. Calcification was defined as >130 Hounsfield (HU) units or areas with at least 1 mm of hyperattenuation in less than three consecutive pixels. The Agatstone method was used to calculate the CACS by calculating the weighted sum of the areas >130 HU.

Statistical Analysis

The distribution of normality for all variables was assessed using the Kolmogorov-Smirnov test. Variables with a normal distribution are presented as mean±standard deviation, and comparisons between groups were conducted using one-way analysis of variance (ANOVA). Categorical variables are expressed as percentages, and the Pearson chi-square test was employed for group comparisons. To identify the specific groups responsible for significant differences in continuous variables, post hoc Tukey-b testing was applied. For categorical variables with significant differences, Bonferroni-corrected z-tests were performed. Gender-specific univariate and multivariate logistic regression analyses were conducted to determine independent predictors of moderate-to-severe CACS in both men and women. A P-value < 0.05 was considered statistically significant. All statistical analyses were carried out using SPSS version 26.0 (IBM Corp., Armonk, NY, USA).

RESULTS

A total of 246 patients were included in the study: 81 patients in Group 1 (CACS 0), 98 patients in Group 2 (CACS between 0 and 99), and 67 patients in Group 3 (CACS ≥100). 134 (54.5%) of the participants in the study were women, and 112 (45.5%) were men. The average age for women was 58.52±9.17 years, while for men it was 52.14±11.43 years. DM was present in 71 patients, comprising 46 (64.8%) women and 25 (35.2%) men. Age (P<0.001), BMI (P<0.001), systolic TA (P<0.001), diastolic TA (P=0.003), coronary critical stenosis rate (P<0.001), DM (P<0.001) and smoking (P<0.001) rates were significantly higher in Group 3 than

Table 1. Baseline demographic and clinical variables of study participants in the coronary artery calcium score groups

Variable	Group 1 (n=81)	Group 2 (n=98)	Group 3 (n=67)	P value
Age (years)	47.92±9.96	58.09±9.72	61.29±7.31	**<0.001[a]**
BMI (kg/m2)	25.53±2.74	27.88±2.10	28.36±2.50	**<0.001[a]**
Systolic BP (mmHg)	121.60±13.40	132.69±9.05	133.19±13.49	**<0.001[a]**
Diastolic BP (mmHg)	78.39±7.45	83.27±5.17	81.86±6.50	**<0.001[a]**
Male gender, n (%)	49 (60.5)	34 (34.7)	29 (43.3)	**0.002[b]**
Critical stenosis >70%	0 (0)	6 (6.1)	17 (25.4)	**<0.001[b]**
HT, n (%)	31 (38.3)	78 (79.6)	47 (70.1)	**<0.001[b]**
DM, n (%)	16 (19.8)	24 (24.5)	31 (46.3)	**0.001[b]**
HL, n (%)	11 (13.6)	53 (54.1)	31 (46.5)	**<0.001[b]**
Smoking, n (%)	20 (24.7)	18 (18.4)	34 (50.7)	**<0.001[b]**
CVD family history, n (%)	15 (18.5)	44 (44.9)	12 (17.9)	**<0.001[b]**

Continuous variables with normal distribution were expressed as mean±standard deviation. Categorical variables are expressed as n (%). BMI=Body mass index, BP=Blood pressure, HT=Hypertension, DM=Diabetes mellitus, HL=Hyperlipidemia, CVD=Cardiovascular disease

[a]One-way ANOVA test; [b]Pearson Chi-Square test.

Table 2. Baseline laboratory and biochemical variables of study participants in coronary artery calcium score groups

Variable	Group 1 (n=81)	Group 2 (n=98)	Group 3 (n=67)	P value
Triglyceride (mg/dL)	125.16±72.82	146.01±87.89	187.46±94.38	**<0.001[a]**
TyG index	4.68±0.27	4.79±0.33	5.17±0.41	**<0.001[a]**
LDL (mg/dL)	119.33±26.50	128.47±25.29	119.17±28.74	**0.031[a]**
HDL (mg/dL)	60.31±14.29	55.84±13.18	54.43±12.72	**0.019[a]**
LDL/HDL	2.08±0.61	2.41±0.71	2.26±0.60	**0.004[a]**
Total cholesterol (mg/dL)	184.72±40.05	192.95±40.31	185.79±34.50	0.305
Total cholesterol/HDL	3.19±0.83	3.58±0.86	3.51±0.69	**0.005[a]**
AIP	-0.0798±0.28	0.0031±0.26	0.1035±0.24	**<0.001[a]**
Uric acid (mg/dL)	4.71±1.03	4.81±1.20	5.04±0.95	0.186
CRP (mg/L)	2.99±1.68	4.06±2.77	4.28±2.85	**0.003[a]**
FBG (mg/dL)	109.25±18.65	120.79±31.50	138.77±49.55	**<0.001[a]**
HbA1c (%)	5.76±0.87	6.25±1.17	6.62±1.57	**<0.001[a]**
Neutrophil/lymphocyte	1.69±0.60	2.44±0.98	2.20±1.17	**<0.001[a]**
Monocyte-HDL ratio	9.25±4.25	7.55±2.37	9.68±4.27	**0.001[a]**

Continuous variables with normal distribution were expressed as mean±standard deviation.

TyG index=Triglyceride-glucose index, LDL=Low density lipoprotein, HDL=High density lipoprotein, AIP=Atherogenic index of plasma, CRP=C-reactive protein, FBG=Fasting blood glucose, HbA1c=Hemoglobin A1c

[a]One-way ANOVA test

in Groups 1 and 2. The findings are shown in Table 1.

No significant difference was observed between Groups 1, 2, and 3 for the parameters t cholesterol and uric acid (P>0.05). HDL was significantly lower in Group 3 than in Group 1 (P=0.026). CRP (P=0.006), HbA1c (P<0.001), and NLR (P=0.003) were significantly higher in Group 3 than in Group 1. Triglyceride (P<0.001), TyG index (P<0.001), AIP (P<0.001), and FBG (P<0.001) values were significantly higher in Group 3 than in Groups 1 and 2. The findings are shown in Table 2.

As a result of univariate and multivariate logistic

Table 3. Univariate and multivariate analyses of moderate-to-severe CAC score predictors in all patients

Variables	Univariate	P value	Multivariate	P value
Age	1.084 (1.049-1.120)	**<0.001**	1.104 (1.053-1.158)	**<0.001**
Triglyceride	1.006 (1.003- 1.009)	**<0.001**	0.999 (0.990-1.007)	0.74
TyG index	24.159 (9.385-62.188)	**<0.001**	37.507 (7.227-194.653)	**<0.001**
AIP	6.510 (2.239-18.933)	**0.001**	0.685 (0.051-9.226)	0.776
FBG	1.017 (1.009-1.025)	**<0.001**	1.002 (0.991-1.014)	0.673
Critical stenosis >%70	9.803 (3.670-26.185)	**<0.001**	3.342 (0.905-12.341)	0.07
DM	2.992 (1.650-5.426)	**<0.001**	0.778 (0.307-1.917)	0.596
Smoking	3.823 (2.102-6.953)	**<0.001**	3.318 (1.466-7.507)	**0.004**

CAC=Coronary artery calcium, TyG index=Triglyseride-glucose index, AIP=Atherogenic index of plasma, FBG=Fasting blood glucose, DM=Diabetes mellitus.

Table 4. Univariate and multivariate analyses of moderate-to-severe CAC score predictors in females

Variables	Univariate	P value	Multivariate	P value
Age	1.083 (1.031-1.136)	**0.001**	1.126 (1.048-1.211)	**0.001**
Triglyceride	1.005 (1.000-1.009)	**0.032**	0.964 (0.937-0.992)	**0.011**
TyG index	28.823 (7.706-107.812)	**<0.001**	35.317 (6.328-187.356)	**0.002**
AIP	3.875 (1.003-14.978)	0.05	8.486 (0.189-380.058)	0.27
FBG	1.011(0.999-1.023)	0.07	0.960 (0.922-1.000)	0.051
Critical stenosis >%70	4.312 (1.143-16.266)	0.031	5.412 (0.695-42.137)	0.107
DM	2.991 (1.372-6.525)	**0.006**	0.439 (0.093-2.080)	0.3
Smoking	2.500 (0.975-6.412)	0.057	1.014 (0.141-7.312)	0.989

CAC=Coronary artery calcium, TyG index= Triglyceride-glucose index, AIP=Atherogenic index of plasma, FBG=Fasting blood glucose, DM=Diabetes mellitus.

regression analyses, age (OR=1.104; 95% C.I. 1.053-1.158, P<0.001), TyG index (OR=37.507; 95% C.I. 7.227-194.653, P<0.001) and smoking (OR=3.318; 95% C.I. 1.466-7.507, P<0.001) were found to be independently associated parameters with the presence of moderate-to-severe CACS in the all patient group. The AIP was not found to be an independently associated parameter with moderate-to-severe CACS (P>0.05). The findings are shown in Table 3.

In gender-specific univariate and multivariate logistic regression analyses, age (OR=1.126; 95% C.I. 1.031-1.136, P<0.001), triglyceride (OR=0.964; 95% C.I. 0.937-0.992, P=0.011) and TyG index (OR=35.317; 95% C.I. 6.328-187.356, P=0.002) were found to be independent predictors of moderate-to-severe CACS in women, and age (OR=1.083; 95% C.I. 1.007-1.165, P=0.032), critical coronary artery stenosis (OR=12.298; 95% C.I. 1.451-104.208, P=0.021) and smoking (OR=8.771; 95% C.I. 1.810-42.501, P=0.007) were found to be independent predictors of moderate-to-severe CACS in men. The AIP was not found to be a parameter independently associated with moderate-to-severe CACS in either women or men (P=0.27, P=0.596, respectively). The findings are shown in Tables 4 and 5.

DISCUSSION

The findings of this study highlight the gender-specific

Table 5. Univariate and multivariate analyses of moderate-to-severe CAC score predictors in males

Variables	Univariate	P value	Multivariate	P value
Age	1.095 (1.044-1.149)	**0.001**	1.083 (1.007-1.165)	**0.032**
Triglyceride	1.008 (1.003-1.013)	**0.001**	1.008 (0.994-1.022)	0.267
TyG index	19.625 (5.092-75.643)	**<0.001**	5.630 (0.618-51.312)	0.125
AIP	18.697 (2.985-117.093)	**0.002**	0.208 (0.001-68.810)	0.596
FBG	1.023 (1.010-1.036)	**<0.001**	1.020 (0.998-1.043)	0.071
Critical stenosis >%70	24.750 (5.043-121.471)	**<0.001**	12.298 (1.451-104.208)	**0.021**
DM	3.012 (1.171-7.748)	**0.022**	0.250 (0.036-1.735)	0.161
Smoking	10.523 (3.612-30.659)	**<0.001**	8.771 (1.810-42.501)	**0.007**

CAC=Coronary artery calcium, TyG index=Triglyceride-glucose index, AIP=Atherogenic index of plasma, FBG=Fasting blood glucose, DM=Diabetes mellitus.

determinants of moderate-to-severe CACS, underscoring the distinct metabolic and clinical pathways contributing to coronary atherosclerosis in men and women. Our results indicate that older age, higher triglyceride levels, and an elevated TyG index are independent predictors of moderate-to-severe CACS in women, whereas in men, older age, severe coronary artery stenosis, and smoking are significant predictors. Notably, AIP was not identified as an independent predictor of moderate-to-severe CACS in either sex, suggesting that other metabolic or inflammatory markers may play a more pivotal role in vascular calcification progression. These findings emphasize the importance of incorporating gender-specific indicators into traditional cardiovascular risk assessment algorithms to enhance the prediction of subclinical atherosclerosis.

In our study, advanced age was independently associated with moderate-to-severe CACS in both men and women. This finding aligns with the Multi-Ethnic Study of Atherosclerosis (MESA), which analyzed data from 6,814 participants aged 45 to 84, free of clinical cardiovascular disease at baseline. The study observed that both the prevalence and extent of CAC increased steadily with advancing age across all racial and ethnic groups [11]. Specifically, the incidence of newly detectable CAC averaged 6.6% per year, with rates of less than 5% per year in individuals under 50, but rising to over 12% in those over 80 [12].

Our study found that severe coronary artery stenosis in men was independently associated with moderate-to-severe CACS. However, this association was not observed in women. This discrepancy may be due to differences in arterial remodeling between sexes [13]. A study by Sangiorgi *et al*. suggests that arterial calcification correlates more with overall plaque burden rather than lumen narrowing, indicating that significant calcification can occur without causing substantial stenosis [14]. This phenomenon, known as positive or outward remodeling, allows the artery to maintain luminal diameter despite progressive atherosclerotic plaque accumulation. This compensatory mechanism involves degradation of the extracellular matrix, activation of matrix metalloproteinases (MMPs), and smooth muscle cell migration, processes that are modulated by hormonal influences such as estrogen. Estrogen has been shown to promote vasodilation, inhibit vascular inflammation, and enhance endothelial function, all of which may contribute to more pronounced remodeling in women [15]. As a result, significant plaque burden may develop with less calcification and without causing luminal narrowing detectable by imaging. This may explain the lack of association between severe coronary stenosis and CAC in our female cohort, despite their metabolic risk profile.

While previous studies have identified an independent association between smoking and moderate-to-severe CACS in women [16, 17], our study found this relationship to be significant in men. Supporting our findings, Lessmann *et al*. [18] reported higher CAC density and prevalence among male heavy smokers compared to female counterparts, noting that CAC levels in women were comparable to those in men a decade younger. However, it's important to consider that this study focused on older heavy smokers undergoing lung cancer screening, which may influence the generalizability of the results.

In our study, AIP was not independently associated with moderate-to-severe CACS. This finding may be explained by the fact that AIP, calculated as the logarithmic ratio of triglycerides to HDL-C, is highly sensitive to short-term metabolic variations such as recent dietary intake, acute insulin resistance, inflammation, or pharmacologic interventions. In contrast, CAC develops gradually over the years and reflects a chronic atherosclerotic burden. This temporal mismatch may limit the utility of AIP in predicting long-term subclinical atherosclerosis as detected by CACS. Similar observations have been reported in previous studies, suggesting that AIP may better predict early atherogenic risk or plaque progression in individuals with low baseline CAC, but its predictive power diminishes in more advanced calcific stages. Notably, previous research has shown that AIP may better predict early atherogenic risk or CAC progression in individuals with low baseline CACS but not in those with moderate-to-severe scores [19]. Therefore, assessing AIP may be more beneficial in the long-term follow-up of patients with initially low CACS.

In our study, the TyG index emerged as an independent predictor of moderate-to-severe CACS in women, underscoring its potential as a valuable marker for assessing cardiovascular risk in this population. This finding is consistent with existing litera-

ture, which highlights the association between the TyG index and subclinical atherosclerosis. For instance, one study demonstrated that an elevated TyG index is associated with an increased risk of both arterial stiffness and CAC, suggesting its utility in predicting subclinical atherosclerosis [20]. Furthermore, research has shown that the TyG index predicts CAC more effectively than other markers of insulin resistance, reinforcing its relevance in cardiovascular risk assessment [21]. Specifically regarding gender, previous studies have emphasized the independent association between the TyG index and both subclinical atherosclerosis and obstructive CAD, particularly in non-diabetic women [22, 23]. In our study, we found an independent association between the TyG index and moderate-to-severe CACS in women, regardless of diabetes status. Similarly, another study reported that the TyG index is associated with carotid atherosclerosis and arterial stiffness, particularly in lean postmenopausal women [24]. These findings suggest the potential of the TyG index as a universal marker for cardiovascular risk assessment across different populations.

Limitations

This single-center, retrospective study limits causal interpretation and reduces the external validity of the findings, particularly when applied to more diverse populations or healthcare settings.

CONCLUSION

In women, moderate-to-severe CACS was independently linked to advanced age, higher triglyceride levels, and an increased TyG index. In contrast, in men, advanced age, severe coronary artery stenosis, and smoking were found to be key predictors. AIP was not independently associated with moderate-to-severe CACS in either gender. Further multicenter, prospective studies are required to examine the influence of the TyG index on subclinical atherosclerosis, especially in women, with attention to gender-related factors.

Ethical Statement

The study was approved by the Siirt University Noninterventional Clinical Research Ethical Committee (Date: 28.11.2024, Decision No: 2024/12/01/04).

Informed Consent

The authors declared that informed consent was not required as the study was a retrospective data analysis.

Authors' Contribution

Study Conception: ÇK, MA, SY, DO; Study Design: ÇK, MA, SY, DO; Supervision: ÇK, MA, SY, DO; Funding: N/A; Materials: ÇK, MA, SY; Data Collection and/or Processing: ÇK, MA, SY, DO; Statistical Analysis and/or Data Interpretation: ÇK, MA; Literature Review: ÇK, MA, SY; Manuscript Preparation: ÇK, DO and Critical Review: ÇK, MA, SY, DO.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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