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Original Article

Associations of Atherogenic Index of Plasma, Triglyceride-Glucose Index, and γ-Glutamyltransferase with Subclinical Coronary Artery Disease: A Cross-Sectional Study

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SUMMARY

Background: Coronary artery disease (CAD) is the leading cause of death worldwide. However, the correlation between the atherogenic index of plasma (AIP), triglyceride-glucose index (TyG), and γ-glutamyl transpeptidase (γGT) with subclinical CAD across different age groups in the Taiwanese population remains unclear.
Methods: This cross-sectional study enrolled 901 participants aged 50–75 years. Medical history taking, physical examination, blood tests, and coronary computed tomography angiography (CCTA) were performed during health checkups. AIP, TyG, and γGT levels were determined. The participants were divided into two groups based on CCTA: those without subclinical CAD and those with subclinical CAD.
Results: Multiple logistic regression analysis suggested that γGT and TyG levels were independently associated with subclinical CAD. Furthermore, γGT was observed to be the only factor independently associated with subclinical CAD in older participants (OR: 1.617, 95% CI: 1.079–2.424, p = 0.020). In comparison, TyG was the only independent factor associated with subclinical CAD in middle-aged participants (OR: 1.323, 95% CI: 1.021–1.714, p = 0.034).
Conclusions: The study results show that AIP, TyG, and γGT can be regular monitoring indices for assessing the risk of subclinical CAD. Additionally, γGT may be more suitable for older persons, while TyG may be more suitable for middle-aged persons.

1. Introduction

Coronary artery disease (CAD) is a leading cause of death globally, responsible for approximately 17.8 million deaths annually worldwide.[1,2] CAD is a pathological condition characterized by atherosclerotic plaque accumulation in the epicardial arteries, resulting in coronary artery stenosis. As atherosclerotic plaques progress, smooth muscle cell death occurs, forming coronary artery calcium (CAC). The presence and extent of CAC serve as important indicators of the severity of coronary atherosclerosis and can predict the presence of subclinical CAD. To effectively communicate the findings from non-contrast CT scans that assess CAC, the Coronary Artery Calcium Data and Reporting System was developed.

Risk factors for CAD include age, sex, cigarette smoking, high blood pressure, diabetes mellitus (DM), lipid levels, and obesity. Dyslipidemia is a critical factor associated with coronary artery stenosis and plays a role in CAD.[3] Previous studies have indicated that high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and triglyceride (TG) levels are predictors of CAD.[4–7] Comprehensive lipid indexes, including atherogenic index of plasma (AIP) and triglyceride-glucose index (TyG), have also been reported as predictors of CAD.[8,9] Obesity has rapidly become more prevalent in developed and developing countries over time.[10,11] Abdominal visceral adipose tissue estimated by multidetector computed tomography is strongly associated with CAC score (CACS).[12] Moreover, liver fat accumulation is more important than general and abdominal fat and can be indicated by γ-glutamyl transpeptidase (γGT) levels.[13] γGT level is strongly associated with CAD owing to an imbalance between oxidant and antioxidant systems.[14]

AIP, TyG, and γGT are strong predictors of CAD. However, to our knowledge, few studies have compared the predictive ability of these markers for CAD. Additionally, it is unclear whether previous conclusions can be generalized to all age groups. Therefore, we explored the correlation between AIP, TyG, and γGT with subclinical CAD by age distribution in Taiwanese adults.

2. Materials and methods

2.1. Study population

This study examined 956 asymptomatic people aged 50–75 who underwent coronary computed tomography angiography (CCTA) during annual health checkups at a health examination center in Northern Taiwan. They were enrolled between January 1, 2008, and

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December 31, 2017. CCTA was used to diagnose subclinical CAD. Data were obtained from medical histories, physical examinations, fasting blood tests, and CCTA. After excluding incomplete data on traditional lipid profiles, body fat (BF), waist circumference (WC), buttock circumference (BC), body mass index (BMI), γGT, as well as those who had angina or myocardial infarction, history of percutaneous coronary intervention or other heart surgery, the final sample consisted of 901 individuals. The study protocol was approved by the Institutional Review Board of Mackay Memorial Hospital (reference number 18MMHIS137) and was conducted by the Declaration of Helsinki. Informed consent was obtained from all patients.

2.2. Study design and variables

This cross-sectional study collected basic information regarding age, sex, blood pressure, routine blood tests, medical history of DM, and personal history of alcohol consumption and cigarette smoking. Indicators of visceral adipose tissue included BF, WC, BC, BMI, and γGT. Plasma lipid profiles (HDL-C, LDL-C, and TG) were also obtained.

AIP was calculated as:[15]

log 10 (*TG* [mmol/L] / *HDL – C* [mmol/L])

TyG was calculated as:[16]

ln (*fasting TG* [mg/dL] × *fasting glucose* [mg/dL] / 2

AIP, TyG, and γGT were processed with Z-transform to Z-scores of zAIP, zTyG, and zγGT, respectively.

2.3. Diagnostic criteria

CAD was defined according to the 1979 WHO diagnostic criteria.[17] CCTA was performed, and the images were analyzed by an experienced radiologist blinded to the study. The primary study outcome was subclinical CAD development, defined as a CACS ≥ 100 Agatston Units and/or ≥ 50% coronary luminal stenosis.[18]

DM was defined as meeting at least one of the following criteria: (1) fasting plasma glucose levels ≥ 126 mg/dL, (2) glycated hemoglobin (HbA1C) ≥ 6.5%, or (3) current use of antidiabetic medications. Alcohol consumption was defined as men and women who drank more than 14 or seven standard drinks per week, respectively. Cigarette smoking was defined as current cigarette smoking.

Metabolic syndrome was defined as having three or more of the following five risk factors: (1) elevated fasting plasma glucose: 100 mg/dl or use of antidiabetic medicines; (2) elevated blood pressure: 130/85 mmHg or use of antihypertensive medicines; (3) elevated triglyceride levels: 150 mg/dl; (4) reduced high-density lipoprotein cholesterol levels: < 50 mg/dl; and (5) central obesity: waist circumference 80 cm.[19]

2.4. Statistical analysis

Participants were divided into two groups based on their CACS: the control group consisted of individuals without subclinical CAD, while the case group included those with subclinical CAD. Continuous variables were expressed as mean ± standard deviation, and categorical variables were presented as counts and percentages. Student's t-test analysis was used for continuous variables, and the chi-square test was used for categorical variables to compare the case and control groups' characteristics. The AIP, TyG, and γGT levels in the case group and control group stratified by age group were presented using boxplots. Binary logistic regression model one was established by adjusting for age and sex to determine the independent risk factors of subclinical CAD. Model two was established by adjusting for age, sex, systolic blood pressure (SBP), LDL-C, DM, BMI, cigarette smoking, and alcohol consumption, and model three was established by model two with forward selection. Subgroup analyses, based on the age cutoff of 65 years old, were also conducted for further assessment. We set the subgroup analysis cutoff at 65 years because this age was generally considered the transition from middle to old age. Hypertension and DM, both significant cardiovascular risk factors, become more prevalent at this age.[20,21] AIP, TyG, and γGT underwent Z transformation, a statistical method to transform raw data into a standard normal distribution, resulting in zAIP, zTyG, and zγGT, respectively. These transformed variables were then applied in Models one, two, and three. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, North, USA). The odds ratios (ORs) and 95% confidence intervals (CIs) were presented, and p values < 0.05 were considered statistically significant.

3. Results

This cross-sectional, observational study enrolled 901 participants who underwent health checkups. Based on CACS, participants were divided into the control group (n = 766) and the case group (n = 135). Additionally, 195 individuals were aged 65 years and older (146 controls and 49 cases), and 706 individuals were aged less than 65 years old (620 controls and 86 cases).

3.1. Baseline clinical and biochemical characteristics

Table 1 shows the study participants' baseline clinical characteristics and laboratory data. The participants' ages ranged from 50 to 75 years. The means of AIP, TyG, and γGT values were significantly higher in the case group than in the control group. Elevated WC, plasma lipid (TG), and decreased HDL-C were also noted. Cigarette smoking, which is a traditional cardiovascular risk factor, also showed significant differences between the two groups. However, this significance was not observed for BF, BC, BMI, or LDL-C levels.

Boxplots in Figure 1 show the distribution of each biomarker in each group, and the p-values for mean comparisons are displayed below each age group. Significant differences in AIP were observed between the control group and the case group in the < 65-year-old and total groups; TyG showed significant differences in the < 65-year-old and total groups. AIP and TyG showed no significant differences in the ≥ 65-year-old group. γGT levels were significantly different in all groups.

3.2. Multivariate-adjusted odds ratios of subclinical CAD for AIP, TyG, and γGT

The correlation between AIP, TyG, and γGT and subclinical CAD was investigated using multiple logistic regression to avoid interference from confounding factors, as shown in Table 2. In model 1, after adjusting for age and sex, multiple logistic regression analysis identified zTyG, zAIP, and zγGT as having a significant association with subclinical CAD. In model 2, logistic regression analysis was performed after adjusting for age, sex, SBP, LDL-C, DM, BMI, alcohol consumption, and cigarette smoking. The results suggested that only zγGT remained independently associated with subclinical CAD. In model 3, a forward stepwise based on model 2 was set up to assess the risk factors for subclinical CAD. The model showed that only zγGT was significantly associated with subclinical CAD.

Table 1
Baseline demographic and clinical characteristics of the study population.

Variables	Control group (n = 766, 85.02%)	Case group (n = 135, 14.98%)	p value
Basic characteristics			
Age (years)	59.5 ± 6.0	62.4 ± 6.4	< 0.001 [a]
Sex			< 0.001 [b]
Male	438 (57.18)	104 (77.04)	
Female	328 (42.82)	31 (22.96)	
SBP (mmHg)	127.7 ± 17.4	130.3 ± 17.3	0.111 [a]
DBP (mmHg)	78.4 ± 10.2	78.1 ± 10.8	0.744 [a]
ALT (IU/L)	28.3 ± 16.5	35.5 ± 59.7	0.005 [a]
Cr (mg/dL)	0.91 ± 0.31	0.98 ± 0.29	0.018 [a]
DM	55 (7.18)	32 (23.70)	< 0.001 [b]
MetS	282 (36.81)	68 (50.37)	0.003 [b]
Smoking	159 (20.76)	50 (37.04)	< 0.001 [b]
Alcohol	186 (24.54)	38 (29.01)	0.277 [b]
Indicators related to visceral adipose			
BF (%)	27.6 ± 6.6	27.4 ± 6.8	0.734 [a]
WC (cm)	86.0 ± 9.5	88.8 ± 9.4	0.001 [a]
BC (cm)	95.1 ± 6.4	95.5 ± 6.4	0.481 [a]
BMI (kg/m^2)	24.7 ± 3.4	25.2 ± 3.6	0.004 [a]
γGT (U/L)	24.8 ± 18.3	34.2 ± 41.6	< 0.001 [a]
Markers of plasma lipid profile			
TG (mg/dL)	133.3 ± 71.5	151.4 ± 92.0	0.010 [a]
LDL-C (mg/dL)	133.8 ± 1.2	133.5 ± 3.4	0.919 [a]
HDL-C (mg/dL)	53.3 ± 15.5	50.0 ± 15.4	0.023 [a]
TyG	9.4 ± 0.6	9.6 ± 0.6	< 0.001 [a]
AIP	0.002 ± 0.30	0.080 ± 0.31	0.006 [a]

Data are presented as the number (%) of patients and the mean ± standard deviation.
[a] The Student's t-test calculated the p-value. [b] The chi-square test calculated the p-value.
Abbreviations: control group, without significant stenosis; case group, significant stenosis; SBP, systolic blood pressure; DBP, diastolic blood pressure; ALT, alanine aminotransferase; Cr, creatinine; DM, diabetes mellitus; MetS, metabolic syndrome; BF, body fat; WC, waist circumference; BC, buttock circumference; BMI, body mass index; γGT, gamma-glutamyl transpeptidase; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TyG, triglyceride-glucose; AIP, atherogenic index of plasma.

3.3. Analysis of the differences between the two subgroups based on age

Among participants aged ≥ 65, only zγGT had a significant association with subclinical CAD. However, among participants aged < 65 years, we observed a significant correlation between zTyG and subclinical CAD.

4. Discussion

In this cross-sectional study, we observed a significant association between AIP, TyG, and γGT and the risk of subclinical CAD after adjusting for age and sex in a Taiwanese adult population. Furthermore, this study's subgroup analysis demonstrated significantly greater γGT values, an indicator related to visceral adiposity, among older people (≥ 65 years old) in the case group. For middle-aged people (50–64 years old), only TyG, a novel predictive marker for CAD, had a stronger association with subclinical CAD after forward selection.

Previous studies have revealed that AIP values reflect the lipoprotein particle size, which may explain its high predictive value for cardiovascular disease.[22] In a previous cross-sectional study, AIP was independently and positively related to the presence and severity of CAD in older individuals and was superior to traditional and other non-traditional lipid indices.[23] However, in this study, the relationship between AIP and subclinical CAD in older individuals was insignificant. Several factors may account for this discrepancy. Many factors are related to AIP levels, including serum uric acid and C-reactive protein (CRP) levels, regions, populations, and pharmacological interventions (such as hormone replacement therapy and vitamin D supplementation).[24]

TyG, a marker calculated from TG and fasting plasma glucose levels, has demonstrated high sensitivity and specificity for detecting insulin resistance, and can be used as a predictor of CAD and adverse cardiovascular events.[25–27] In a retrospective study with 680 patients, Si et al. concluded that an increased TyG index is an independent risk factor for CAD with type 2 DM. Furthermore, its risk is higher in middle-aged than in older subgroups. This is similar to the results of our subgroup analysis.[28] We found a significant association between TyG and subclinical CAD in middle-aged individuals and an insignificant relationship in older people.

In addition to being an indicator of liver diseases, γGT is also significantly associated with higher visceral fat and can be helpful as a sensitive and early biomarker of visceral adiposity.[29] Visceral adipose tissues also play an essential role in cardiometabolic risk.[30] Elevated γGT levels can cause an imbalance between the oxidant and antioxidant systems, making it strongly associated with CAD.[14]

We found that γGT is significantly associated with subclinical CAD in adults in Taiwan. In a 24-year prospective follow-up study of 6997 middle-aged people (aged 40–59 years) with no history of CAD or DM in 24 British towns, elevated γGT was found to be independent of the established CAD risk factors.[31] Moreover, our subgroup analysis showed an even stronger association in older individuals. Many factors may explain the association between γGT and CAD in different age groups. The level of γGT may reflect oxidative stress and nonalcoholic fatty liver disease.[32] Therefore, lifestyle and underlying diseases that lead to varying degrees of association between γGT and CAD in different age groups should also be considered.[31]

Notably, the LDL-C level in the case group was not elevated in this study. The LDL-C level has been considered a significant risk factor for CAD. However, several studies have shown that LDL-C concen-

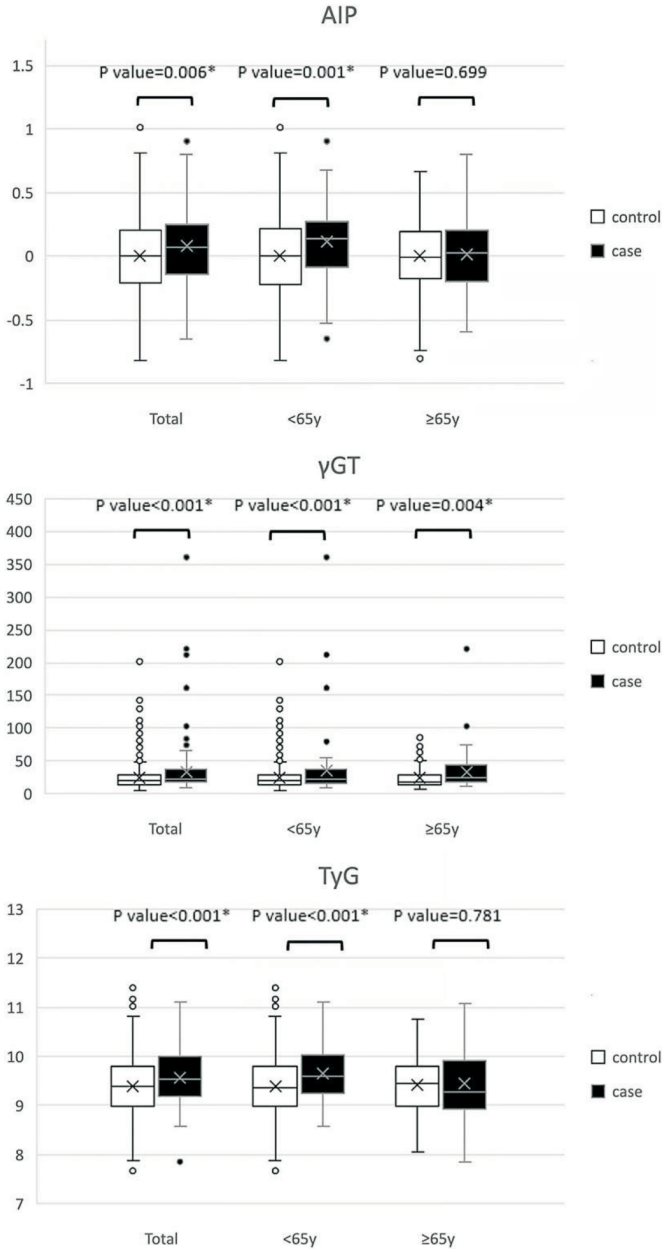

Figure 1. Comparison of AIP, γGT, and TyG levels between case and control groups stratified by age group. AIP, atherogenic index of plasma; γGT, γ-glutamyltransferase; TyG, triglyceride-glucose index. * p value < 0.05.

tration is not always high in patients with acute coronary syndrome.[33] LDL-C is a heterogeneous mixture of particles with different densities and sizes, and sdLDL-C is more atherogenic. As a result, LDL-C alone may not correctly reflect the risk of CAD; therefore, we can utilize other noninvasive indicators as a reference to assess CAD.

This study had several limitations. First, a selection bias might exist, and the results might not be generalizable to other populations. Our participants voluntarily underwent health checkups and might have been more aware of their health. Additionally, most of them lived in the capital city of Taiwan, where they had good access to healthcare. Second, this study's sample size was small, and the number of participants in the subgroups based on age (65 years) was not similar between the two groups. Third, there are many risk factors for CAD, and it is not easy to consider them all using a single model. Moreover, participants' information was collected during health checkups, which did not include records of their current medications, including antihyperlipidemic agents. In future studies, researchers should explore the effects of antihyperlipidemic therapy on serum lipid markers, particularly AIP, TyG, and gGT, and their relationship with CAD.

Despite these limitations, this pilot study aimed to compare the correlation between AIP, TyG, and γGT and the risk of subclinical CAD in different age groups (50–65 and 65–75 years old). Moreover, CCTA data from people who underwent health checkups are valuable because it is uncommon for healthy individuals to undergo CCTA. These findings suggest that AIP, TyG, and γGT could serve as effective screening instruments to identify asymptomatic CAD cases and aid early prevention of complications.

This study's findings show that AIP, TyG, and γGT can be used as regular monitoring indices for the risk of subclinical CAD. These noninvasive clinical markers can detect subclinical CAD early. Furthermore, the study results highlight the age-specific relevance of γGT and TyG as biomarkers for assessing the risk of subclinical CAD. Specifically, γGT appears more suitable for older individuals, whereas TyG may be more appropriate for middle-aged individuals.

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Table 2
Binary logistic regression analysis of the presence of subclinical CAD.

	(z)TyG		(z)AIP		(z)γGT	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Total (n = 901)						
Model 1	1.320 (1.088–1.602)	0.005*	1.237 (1.010–1.514)	0.040*	1.284 (1.090–1.513)	0.003*
Model 2	1.144 (0.917–1.427)	0.233	1.118 (0.885–1.412)	0.349	1.242 (1.042–1.480)	0.016*
Model 3					1.248 (1.050–1.483)	0.012*
≥ 65 years old (n = 195)						
Model 1	1.068 (0.767–1.489)	0.696	1.056 (0.744–1.499)	0.761	1.594 (1.055–2.409)	0.027*
Model 2	0.929 (0.634–1.360)	0.704	0.978 (0.655–1.460)	0.912	1.605 (1.043–2.470)	0.031*
Model 3					1.617 (1.079–2.424)	0.020*
< 65 years old (n = 706)						
Model 1	1.463 (1.150–1.862)	0.002*	1.325 (1.031–1.702)	0.028*	1.227 (1.027–1.466)	0.024*
Model 2	1.292 (0.981–1.702)	0.069	1.202 (0.899–1.608)	0.214	1.161 (0.954–1.413)	0.136
Model 3	1.323 (1.021–1.714)	0.034*				

Model 1 (Z transformation): adjusted for age, sex. Model 2 (Z transformation): adjusted for age, sex, DM, BMI, SBP, LDL-C, cigarette smoking, alcohol consumption. Model 3 (Z transformation): model 2 with forward stepwise. * Statistical significance.
Abbreviations: BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; LDL-C, Low-density lipoprotein cholesterol; OR, odds ratio; SBP, systolic blood pressure; zAIP, Z-score of the atherogenic index of plasma; zγGT, Z-score of the gamma-glutamyl transpeptidase; zTyG, Z-score of the triglyceride-glucose.

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Declaration of any potential financial and non-financial conflicts of interest

The authors declare that they have no conflict of interest.

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