Elevated TyG Index Predicts Progression of Coronary Artery Calcification

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OBJECTIVE

To investigate the triglyceride-glucose (TyG) index association with coronary artery calcification (CAC) progression in adult Koreans.

RESEARCH DESIGN AND METHODS

Various cardiovascular risk factors and anthropometric profiles were assessed in 1,175 subjects who previously had a CAC evaluation at least twice by multidetector computed tomography in a health care center. The TyG index was determined using ln(fasting triglycerides [mg/dL] × fasting glucose [mg/dL]/2). The CAC progression was defined as either incident CAC in a CAC-free population at baseline or an increase of ≥2.5 units between the square roots of the baseline and follow-up coronary artery calcium scores (CACSs) of subjects with detectable CAC at baseline.

RESULTS

CAC progression was seen in 312 subjects (27%) during 4.2 years follow-up. On the basis of the TyG index, subjects were stratified into three groups. Follow-up CACS and incidence of CAC progression were markedly elevated with rising TyG index tertile. Logistic regression analysis adjusted for various risk factors revealed an odds ratio for CAC progression of 1.82 (95% CI 1.20–2.77; $P \leq 0.01$) when the highest and lowest TyG index tertiles were compared.

CONCLUSIONS

The TyG index is an independent predictor of CAC progression.

Understanding the progression of cardiovascular disease (CVD) is important because the disease can lead to severe morbidity and mortality. An important risk factor for CVD is coronary artery calcification (CAC), and cardiovascular risk is commonly assessed by coronary artery calcium score (CACS), as determined by computed tomography (CT) (1–4).

Insulin resistance (IR) is one of the major factors that leads to CVD, and several earlier studies have shown a relationship between IR and CAC (5,6). A reliable surrogate marker of IR was recently suggested to be the triglyceride-glucose (TyG) index, which is calculated using fasting triglyceride (TG) and fasting glucose measurements (7–9).

Several previous studies indicated that the TyG index is associated with CAC and CVD (10–14); however, the results were inconsistent. In addition, although CAC progression is a powerful predictor of mortality compared with baseline CACS and traditional cardiovascular risk factors (15), no previous study has investigated the relationship between TyG index and CAC progression in adults. Therefore, we

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examined the relation between baseline TyG index level and CAC progression in a population of Korean adults.

RESEARCH DESIGN AND METHODS

Study Population

In this retrospective longitudinal study, subjects comprised 9,581 Korean adults who, as part of a self-referred checkup program, underwent cardiac CT examination at the Gangnam Severance Hospital Health Promotion Center in Seoul, Korea, between July 2006 and April 2018. Initially, 1,329 individuals who had undergone at least two cardiac CT scans were enrolled. Patients with an elevated TG level (≥400 mg/dL) (*n* = 38), any malignancy (*n* = 9), acute inflammatory disease (*n* = 4), renal disease (*n* = 4), missing data (*n* = 11), or a history of previous cerebrovascular event, myocardial infarction, or angina (*n* = 73) were excluded. Patients taking medications to lower TGs (e.g., fenofibrate or omega-3) (*n* = 15) were also not included in the study. Finally, 1,175 subjects were analyzed (Fig. 1). This study was approved by the institutional review board of Yonsei University College of Medicine.

Anthropometric Measurement and Laboratory Assessment

Subjects wore light clothing without shoes during body weight measurements. BMI was determined by dividing body weight in kilograms by height in meters squared. Measurements of systolic blood pressure (SBP) and diastolic blood pressure (DBP) were taken by trained nurses with an automatic blood pressure monitor (HEM-7080IC; Omron Healthcare, Lake Forest, IL).

All subjects were examined after fasting for 12 h. Blood chemistry (TG, total cholesterol [TC], HDL cholesterol [HDL-C], and fasting plasma glucose [FPG]) was assessed using a Hitachi 7600-120 automated chemistry analyzer (Hitachi, Tokyo, Japan). Calculation of LDL cholesterol (LDL-C) was done using the Friedewald equation. TyG index was calculated as ln(fasting TGs [mg/dL] × fasting glucose [mg/dL]/2).

Data on lifestyle habits, personal medical information, and medication history were collected with a questionnaire. A subject was considered a current smoker if he or she smoked regularly in the past 6 months. A subject who consumed alcoholic drinks more than three times a week was considered a current drinker. Exercise with moderate intensity for more than a half hour at least three times a week was defined as a regular exerciser. A subject was considered to have diabetes on the basis of a previous history of diabetes, current use of antidiabetic medications, or ADA diagnostic guidelines. An SBP or a DBP ≥140/90 mmHg and antihypertensive medication use were considered as criteria for hypertension.

CACS Measurement

A multidetector CT scanner (Philips Brilliance 64; Philips Medical Systems, Best, the Netherlands) was used to measure CACS. A prospective ECG gating protocol with a step-and-shoot technique was used (16). All subjects were in the supine position and held their breath during the imaging process. One of three trained radiologists, all of whom were blinded to the laboratory and clinical information, performed the analysis of coronary CT images. The CACS was quantified automatically with dedicated software, and the severity was assessed using the Agatston score (Aquarius Workstation; TeraRecon, Foster City, CA). A CACS >0 was defined as CAC. CAC progression was defined as either *1*) incident CAC, indicating a baseline Agatston score of 0 but detectable CAC at follow-up examination in a population free from CAC at baseline (17) or *2*) an increase of ≥2.5 units between baseline and the final square root of CACSs in subjects with detectable CAC at baseline (18). Change in square root–transformed CAC ($\Delta\sqrt{}$transformed CAC) was annualized with the interscan period (annualized $\Delta\sqrt{}$transformed CAC).

Statistical Analysis

Continuous variables are shown as mean ± SD; χ^2 tests were done to compare categorical variables, expressed as percentages. ANOVA was used for between-group analyses. The association between CAC progression and the TyG index was assessed by logistic regression after adjustment for any potential confounders. In the multivariable model, the following covariates were chosen because of their clinical importance and statistical significance in the univariable analysis: age, sex, BMI, SBP, LDL-C, HDL-C, exercise, alcohol, smoking, presence of diabetes or hypertension, use of statins or aspirin, and baseline ln(CACS + 1). In addition, we further adjusted for change in BMI, SBP, LDL-C, HDL-C, and TyG index and change in whether taking drugs for diabetes and hypertension, statins, or aspirin. In separate models, we assessed the multivariable-adjusted relationship of TyG index with CAC incidence and CAC progression of subjects with detectable CAC at baseline (increase ≥2.5 units between baseline and final square root of CACSs). Statistical analyses were done using SPSS version 23.0 software (IBM Corporation, Chicago, IL), and $P < 0.05$ was considered statistically significant.

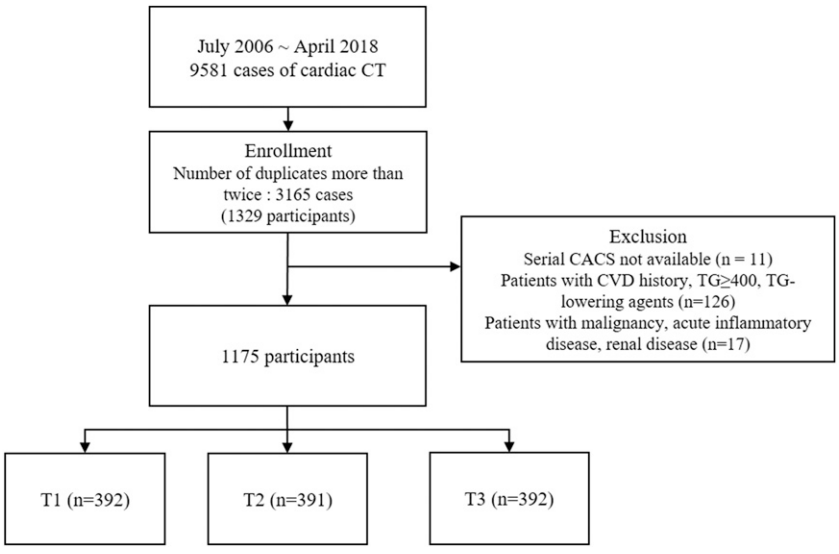

Figure 1—Study flow.

RESULTS

Baseline Characteristics

The mean age of the 1,175 subjects at baseline was 51 ± 7 years, and 71.1% of subjects were men (*n* = 835). The included subjects were stratified into three groups on the basis of TyG index level. The biochemical parameters and clinical characteristics of the study subjects are presented in Table 1. TC, LDL-C, FPG, and TG levels and BMI, DBP, and SBP were elevated, whereas HDL-C was decreased in subjects with a high TyG index. Likewise, the high TyG index group had more hypertension, diabetes, alcohol consumption, and current smoking. Baseline CACS values were also higher with a higher TyG index. These trends were still observed after follow-up (Supplementary Table 1).

Comparison of Variables in Relation to the Degree of CAC Progression

Subjects were stratified into three groups on the basis of the severity of CAC progression (any increase in CACS was considered as CAC progression): no progression, CAC progression of 0 to <100, CAC progression of ≥100 (Table 2). Subjects who showed more CAC progression were of older age; more often men; more likely to have elevated baseline SBP, DBP, BMI, FPG, TG, hypertension, diabetes, exercise, and baseline CACS; and more likely to have a lower HDL-C. When TyG index level was compared according to CAC progression severity, TyG index level increased significantly as CAC severity increased from a CACS of 0 to ≥100 (Table 2).

Table 1—Characteristics of participants according to TyG index tertiles

	T1	T2	T3	*P* value
n	392	391	392	
Age (years)	51.9 ± 8.1	52.0 ± 7.8	51.5 ± 7.2	0.67
Sex (*n* male/*n* female)	192/200	293/98	350/42	
SBP (mmHg)	119.2 ± 15.6	124.9 ± 15.9	127.1 ± 15.0	<0.01
DBP (mmHg)	74.0 ± 10.0	78.5 ± 9.7	80.4 ± 8.7	<0.01
BMI (kg/m^2)	22.9 ± 2.7	24.3 ± 2.8	25.3 ± 2.8	<0.01
FPG (mg/dL)	89.4 ± 10.6	98.7 ± 13.1	105.9 ± 21.2	<0.01
TC (mg/dL)	188.4 ± 31.2	196.3 ± 36.6	204.9 ± 36.8	<0.01
TG (mg/dL)	64.9 ± 14.0	106.2 ± 18.2	194.2 ± 56.8	<0.01
HDL-C (mg/dL)	58.0 ± 12.3	50.2 ± 11.7	44.0 ± 9.5	<0.01
LDL-C (mg/dL)	116.7 ± 30.0	126.0 ± 31.9	130.0 ± 34.1	<0.01
TyG index	7.94 ± 0.26	8.54 ± 0.14	9.18 ± 0.29	<0.01
Hypertension	68 (17.3)	117 (29.9)	132 (33.8)	<0.01
Diabetes	8 (2.0)	28 (7.2)	62 (15.9)	<0.01
Statin use	8 (2.0)	17 (4.3)	19 (4.9)	0.09
Alcohol	46 (11.7)	63 (16.1)	79 (20.2)	<0.01
Smoking	20 (5.1)	46 (11.8)	67 (17.1)	<0.01
Exercise	62 (15.8)	87 (22.3)	62 (15.8)	0.03
Baseline CACS	14.0 ± 56.0	25.7 ± 80.1	28.8 ± 94.0	0.02
Categorical CACS				<0.01
0	305 (77.8)	271 (69.3)	267 (68.1)	
0 to ≤10	25 (6.4)	30 (7.7)	26 (6.6)	
>10	62 (15.8)	90 (23.0)	99 (25.3)	
Follow-up CACS	28.0 ± 89.7	49.9 ± 138.9	74.9 ± 208.8	<0.01
Categorical CACS				<0.01
0	280 (71.4)	237 (60.6)	202 (51.5)	
0 to ≤10	17 (4.3)	26 (6.6)	29 (7.4)	
>10	95 (24.2)	128 (32.7)	161 (41.1)	
Baseline ln(CACS + 1)	0.72 ± 1.50	1.10 ± 1.84	1.15 ± 1.85	<0.01
Follow-up ln(CACS + 1)	1.07 ± 1.86	1.55 ± 2.14	1.96 ± 2.25	<0.01
Observation time (years)	4.2 ± 2.2	4.0 ± 2.1	4.4 ± 2.3	0.06
CAC progression	69 (17.6)	100 (25.6)	143 (36.5)	<0.01

Data are mean ± SD or *n* (%). Alcohol, moderate drinking; CAC progression, incident CAC or increase ≥2.5 units between baseline and final square root of CACSs; exercise, regular exercise of moderate intensity; smoking, current smoker.

CACS Change According to TyG Index Level

Table 1 presents the follow-up CACS according to TyG index. The average follow-up period was 4.2 ± 2.2 years, and there was no significant difference among the three groups. Follow-up CACS and incidence of CAC progression increased significantly with a rise in TyG index tertile.

Figure 2 shows that both the $\Delta\sqrt{}$transformed CACSs (tertile 1 [T1] 0.92 ± 2.37, T2 1.30 ± 2.87, T3 2.26 ± 4.03; $P < 0.01$) and annualized $\Delta\sqrt{}$transformed CACSs (T1 0.20 ± 0.67, T2 0.36 ± 1.32, T3 0.48 ± 0.84; $P < 0.01$) increased across tertiles of TyG index at baseline. The group with a higher TyG index had greater $\Delta\sqrt{}$transformed CACSs and annualized $\Delta\sqrt{}$transformed CACSs.

Association Between CAC Progression and TyG Index

Univariable logistic regression analysis indicated that age, male sex, BMI, SBP, DBP, HDL-C, baseline CACS, and presence of hypertension or diabetes were statistically associated with CAC progression. In addition, increasing TyG index tertile was significantly correlated with risk of CAC progression (Supplementary Table 2). Taking T1 as the reference, multivariable logistic regression analysis revealed that the TyG index levels for T2 and T3 increased the odds ratios for CAC progression (Table 3). This relationship remained statistically significant after adjustment for sex, age, and other risk factors. In addition, after adjusting for confounding variables, including change in BMI, SBP, LDL-C, HDL-C, and TyG index and change in whether taking drugs for diabetes and hypertension, statins, or aspirin, these relationships were statistically significant (Supplementary Table 3).

Furthermore, we performed the multivariable logistic regression analysis separately for incident CAC and CAC progression of subjects with detectable CAC at baseline. In both groups, TyG index was an independent predictive marker (Supplementary Table 4).

CONCLUSIONS

In the current study, we noticed a significant association between CAC progression and TyG index in Korean adults. Even after adjusting for cardiovascular risk factors, there was an independent association of TyG index with CAC

Table 2—Baseline characteristics of subjects by change in CACS at follow-up

	No change	0 < CACS change <100	CACS change ≥100	*P* value
n	755	331	89	
Age (years)	50.0 ± 7.0	54.4 ± 8.0	56.8 ± 8.0	<0.01
Sex (*n* male/*n* female)	479/276	274/57	82/7	
SBP (mmHg)	121.8 ± 15.7	126.9 ± 15.2	128.4 ± 17.0	<0.01
DBP (mmHg)	76.5 ± 9.8	79.3 ± 9.6	80.6 ± 9.8	<0.01
BMI (kg/m^2)	23.8 ± 3.0	24.7 ± 2.6	25.3 ± 2.8	<0.01
FPG (mg/dL)	95.6 ± 15.6	101.5 ± 17.6	105.0 ± 22.0	<0.01
TC (mg/dL)	195.5 ± 35.1	200.0 ± 35.9	192.8 ± 38.3	0.09
TG (mg/dL)	116.7 ± 62.2	130.1 ± 67.9	133.7 ± 67.1	<0.01
HDL-C (mg/dL)	51.7 ± 13.2	49.4 ± 11.6	48.1 ± 10.1	<0.01
LDL-C (mg/dL)	122.7 ± 31.7	128.9 ± 33.2	119.9 ± 34.5	<0.01
TyG index	8.49 ± 0.57	8.66 ± 0.54	8.72 ± 0.51	<0.01
Hypertension	164 (21.7)	112 (33.8)	41 (46.6)	<0.01
Diabetes	39 (5.2)	43 (13.0)	13 (18.2)	<0.01
Statin use	21 (2.8)	19 (5.7)	4 (4.5)	0.06
Alcohol	121 (16.0)	47 (14.2)	20 (22.7)	0.15
Smoking	86 (11.4)	34 (10.3)	13 (14.8)	0.49
Exercise	119 (15.8)	71 (21.5)	21 (23.9)	0.03
Baseline CACS	3.67 ± 22.29	34.31 ± 87.30	142.82 ± 176.54	<0.01
Baseline ln(CACS + 1)	0.24 ± 0.90	1.86 ± 1.89	4.07 ± 1.72	<0.01

Data are mean ± SD or *n* (%). Alcohol, moderate drinking; exercise, regular exercise of moderate intensity; smoking, current smoker.

progression. To our knowledge, this study is the first to reveal a longitudinal association of TyG index and CAC progression. These results also demonstrate an association between increased TyG index level and traditional CVD risk factors, which is consistent with previous studies (10–12,19–21).

CAC prevalence is considered a surrogate marker for predicting CVD risk; we reported a significant association of the TyG index with CAC prevalence in a previous cross-sectional study (10). Because of this, a causal relationship between TyG index and CAC could not be demonstrated. In the current study, the baseline and follow-up CACSs increased according to TyG index level, and subjects who experienced CAC progression during follow-up had a significantly higher baseline TyG index. Besides, we also showed that the TyG index was independently associated with CAC progression, regardless of conventional risk factors. Recent cross-sectional reports have demonstrated a positive correlation between TyG index and CAC (10,11,14); however, earlier studies did not address the relationship between CAC progression and TyG index.

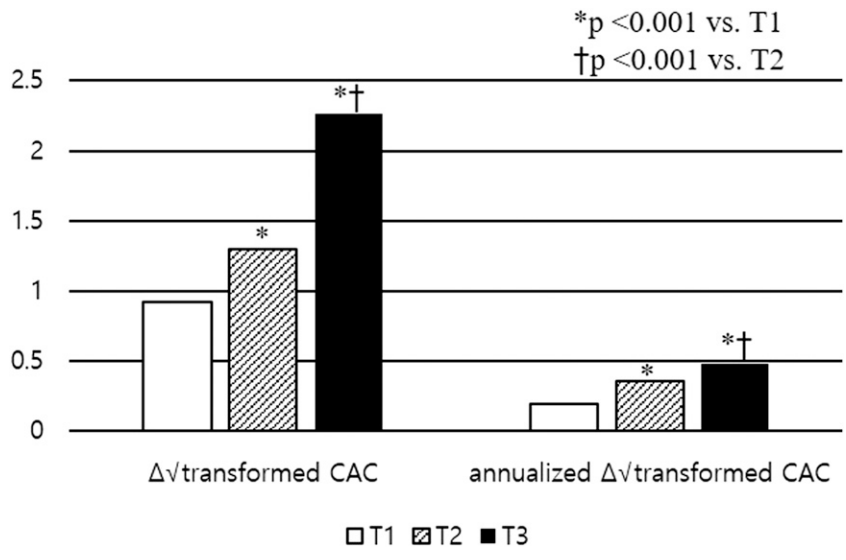

Figure 2—Change of CAC according to TyG index tertiles.

Although the mechanism underlying the association is still unclear, the TyG index is a surrogate marker of IR, which may be important. Many studies have indicated the importance of IR not only in atherogenesis but also in advanced plaque progression by promoting apoptosis of macrophages, endothelial cells, and vascular smooth muscle cells (22–26). Furthermore, IR has been shown to be independently associated with CAC progression. In a population-based study performed by Yamazoe et al. (27), IR, assessed as HOMA-IR, was an independent predictor of CAC progression in Japanese men without diabetes. Sung et al. (28) also showed that HOMA-IR was independently associated with an increase in CAC. In contrast, such an independent association between IR and CAC progression was not observed in some studies. Blaha et al. (29) reported an association between HOMA-IR and CAC progression and incidence, but it was not predictive after adjustment for the components of metabolic syndrome and other established risk factors. Lee et al. (30) observed no association of HOMA-IR with CAC progression in a community-based population without clinical coronary artery disease. These discrepancies call for further large-scale prospective studies to clarify this relationship and the involved mechanisms.

Our study has several limitations. The results may not be generalizable because most subjects were relatively young and male. Only subjects who repeated coronary CT scans were enrolled in this study, so there may be a selection bias. Subjects who had higher CVD risk were more likely to be enrolled in the study. The follow-up period was short and varied, even though baseline characteristics differed among CAC progression groups. Although we statistically adjusted for confounding factors in our multivariable regression, the adjustment may not have entirely removed confounding factors. The potential effects of medications taken for hypertension and diabetes on CAC progression could not be eliminated in this study. Because

Table 3—CAC progression according to TyG index tertiles

	OR (95% CI)			
TyG index	T1	T2	T3	*P* value for trend
Model 1	1.00	1.61 (1.14–2.27)	2.69 (1.93–3.75)	<0.01
Model 2	1.00	1.36 (1.94–1.96)	2.13 (1.49–3.06)	<0.01
Model 3	1.00	1.15 (0.78–1.71)	1.82 (1.20–2.77)	<0.01

Model 1: unadjusted. Model 2: adjusted for age and sex. Model 3: model 2 + BMI, SBP, LDL-C, HDL-C, exercise, alcohol, smoking, presence of diabetes and hypertension, use of statins and aspirin, and baseline ln(CACS + 1). OR, odds ratio.

this was an observational study, some of the responses to the questionnaire on medication history may have been inaccurate, and there was a lack of information on dose and class of antihypertensive and antidiabetic drugs. Therefore, the effects of hypertension and diabetes medications were not considered, and changes in whether taking drugs for diabetes and hypertension, statins, or aspirin were considered instead in the analysis. Finally, HOMA-IR was not analyzed and compared with TyG index because insulin levels were not measured in the general health checkup. Despite these limitations, this study has significant implications that are clinically relevant because it is the first to investigate the association between TyG index and CAC progression.

In this study, an independent association of elevated TyG index level with CAC progression was seen regardless of other conventional CVD risk factors. The TyG index might be an important predictor of CAC progression, reflecting cardiovascular risk.

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