

Assessment of Various Insulin Resistance Surrogate Indices in Thai People with Type 2 Diabetes Mellitus

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Abstract

Objective. To compare insulin surrogate indices with the homeostasis model assessment of insulin resistance (HOMA-IR) in Thai people with type 2 diabetes (T2D).

Methodology. A cross-sectional study of 97 individuals with T2D was done to determine the association between HOMA-IR and seven surrogate indices for insulin resistance. IR was defined as HOMA-IR ≥ 2.0 . The indices included Waist Circumference (WC), Waist-to-Hip Ratio (WHR), Waist-to-Height Ratio (WHtR), Triglyceride-Glucose (TyG) index, estimated Glucose Disposal Rate (eGDR) calculated by WC, BMI, and WHR.

Results. A total of 97 subjects with T2D (36.1% female, mean age 61.7 ± 12.0 years, BMI 26.4 ± 3.7 kg/m², A1C $6.9 \pm 1.2\%$) were studied. The TyG index showed a positive association with HOMA-IR, while eGDR exhibited a negative association. TyG index had the strongest correlation with IR ($r = 0.49$), while various eGDR formulas showed weaker negative correlations ($r = 0.12-0.25$). However, subgroup analysis in individuals with T2D and coronary artery disease (CAD) showed that only eGDR-WC and eGDR-BMI demonstrated a significant correlation with triple vessel disease.

Conclusion. The TyG index was a useful and simple marker for identifying the presence of IR in Thai people with T2D. Future longitudinal studies are warranted to demonstrate the prediction value of cardiovascular outcomes.

Key words: *Insulin resistance, Surrogate Markers, HOMA-IR, Triglyceride-Glucose (TyG) index, estimated Glucose Disposal Rate (eGDR)*

INTRODUCTION

Insulin resistance (IR) is a major risk factor for developing diabetes complications, especially cardiovascular disease (CVD) among people with type 2 diabetes (T2D).¹ Insulin receptors and their downstream insulin signaling-related molecules play various pathological mechanisms in vascular endothelial cells and macrophages.² Changes in insulin signaling activity leads to the onset and progression of atherosclerosis. Although insulin resistance develops more commonly in people with obesity, not all insulin-resistant persons are obese.³ Other factors leading to insulin resistance could put non-obese people at risk of CVD events. Therefore, several IR surrogate indices have been created in an attempt to quantify the severity of IR in people with and without diabetes.⁴⁻⁷ The Homeostatic Model Assessment (HOMA-IR) has been widely used in clinical research since 1985 to quantify IR indirectly as the hyperinsulinemic-euglycemic clamp technique is too complex to be used in clinical settings.⁴

However, the HOMA-IR model requires insulin measurement which can be a limitation for low- and middle-income countries (LMICs). Several alternative IR surrogate markers including anthropometry and body composition,⁸⁻¹⁰ triglyceride-glucose index (TyG),¹¹ and estimated Glucose Disposal Rate (eGDR)¹² have subsequently been developed and validated in population-based studies conducted in various parts of the world. The availability of fasting lipid profiles and the known role of hepatic triglyceride content as a strong determinant of insulin resistance in both liver and muscle led to the creation of the TyG index in 2008 by using fasting plasma glucose (FPG) and triglyceride (TG) levels to provide an estimate of IR.¹¹ Later studies also found that the TyG index could be an independent predictor of unfavorable cardiovascular outcomes in people with T2D.¹³⁻¹⁵ On the other hand, eGDR which was proposed earlier in 2000 by using the available clinical factors such as waist circumference (WC), presence or absence of hypertension, and glycated hemoglobin (A1C) was developed to estimate IR in people with type

1 diabetes (T1D).¹² The utility of eGDR as a measure of IR was validated in more diverse populations, including predicting survival in people with T2D.¹⁶ The use of these instruments for identifying high-risk individuals with IR could assist clinicians in prioritizing interventions in resource-constrained settings. Moreover, the IR-associated co-morbidities could also be targeted to prevent or delay the progression to advanced stages in people with IR.

Unfortunately, to date, there have been few cohort studies conducted in the Southeast Asian population to assess various insulin resistance surrogate indices among the general population. Furthermore, there has been no dedicated study among the Southeast Asian population to evaluate various insulin resistance surrogate markers in individuals with type 2 diabetes, with or without atherosclerotic cardiovascular disease (ASCVD). Moreover, the strength of these surrogate markers could be different according to the ethnicity of the study populations. In the present study, we aim to evaluate various simple insulin surrogate indices with the HOMA-IR in Thai people with T2D and compare the performance of TyG and eGDR in predicting the severity of coronary artery disease (CAD) among T2D with CAD.

METHODOLOGY

This cross-sectional study included Thai adults with T2D who had regular follow-up visits at Theptarin Hospital, a tertiary center in diabetes care in Bangkok, Thailand, between January and June 2023. Participant inclusion criteria included (1) diagnosis of T2D and (2) completed surveillance of diabetes complications. All eligible patients were sequentially invited to participate in the study through consecutive non-random sampling. Exclusion criteria included (1) age <15 years old; (2) participants who are unable to accurately obtain anthropometric measurements; (3) active malignancy or malignant diseases within 1 year of completed treatment (4) changes in weight $\geq 5\%$ within 6 months before enrollment (5) fasting plasma insulin <2 mU/L or >100 mU/L. This study was approved by the Institutional Review Board Committee of Theptarin Hospital (EC No.02-2022). The study was registered with the clinical trial registry on 04/08/2022, with identifier number TCTR20220804006. Before participating in the study, all participants provided written informed consent.

Sample size calculation

The prevalence of insulin resistance among Thai adults was 25.1%.¹⁷ According to the study by Guerrero-Romero et al., the TyG index showed sensitivity and specificity rates of 96.5% and 85.0% for diagnosing insulin resistance, respectively.¹⁸ Using the Buderer Formula,¹⁹ minimum sample sizes of 52 and 66 were calculated, assuming α of 0.05, β of 0.80, and a 95% confidence interval.

For eGDR-WC, sensitivity and specificity were reported at 83.3% and 79.8% respectively,¹² resulting in minimal

sample sizes of 214 for sensitivity and 83 for specificity. Regarding eGDR-WHR, specificity was 83.3% and sensitivity was 86.7%,¹² leading to minimal sample sizes of 72 and 178. To the best of our knowledge, the eGDR-BMI has recently been proposed to be associated with insulin resistance; however, its sensitivity and specificity have not yet been demonstrated. In accordance with this sample size calculation, the recommended sample size was 214 participants. Due to budgetary and time constraints imposed by the grant and the associated laboratory costs, we were only able to enroll the maximum number of cases feasible within these limitations.

Data collection and definitions

Participants underwent routine clinical physical examination, which included the collection of overnight fasting venous blood samples and measurement of weight, height, waist circumference, and resting blood pressure. Weight was determined without shoes by using an automatic electronic scale (Tanita Corp., Tokyo, Japan) to the nearest 100 grams. Standing height was determined without shoes by a wall-mounted stadiometer. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Waist circumference (WC) was measured in the horizontal plane midway between the lowest ribs and the iliac crest. Hip circumference was measured across the broadest part of the buttocks. Waist-related anthropometric measures including WC, waist-to-hip ratio (WHR), and waist-to-height ratio (WHtR) as predictors of IR were studied. The data on patient characteristics, smoking status, glycemic and lipid management, insulin usage, diabetic complications, and co-morbidities were collected. In patients with established ASCVD, significant CAD was defined as more than 50% angiographic diameter stenosis in one or more of the epicardial coronary arteries. Triple-vessel disease was defined as the involvement of any three or more arteries.

The prevalence of IR was estimated by the HOMA-IR method which was calculated with the formula: fasting plasma glucose (mmol/L) times fasting serum insulin (mU/L) divided by 22.5. Based on a previous study in the Asian population, insulin resistance was defined by a HOMA-IR index ≥ 2.0 , which is the value that predicts the development of diabetes more accurately and correlates with the hyperglycemic-hyperinsulinemic clamp method.²⁰ Participants with a HOMA-IR ≥ 2.0 were categorized into the insulin-resistant group, and patients with a HOMA-IR <2.0 were categorized into the insulin-sensitive group.

Clinical laboratory analyses

Fasting plasma glucose concentrations (FPG) were determined using the hexokinase method. Fasting plasma insulin concentrations were measured using a solid-phase, two-site chemiluminescent immunometric assay (Immulite 1000, Insulin) with an inter-assay coefficient of variation at 3.3%. Plasma TG concentrations were determined using

standardized enzymatic glycerol phosphate oxidase assay procedures.

TyG index was calculated according to the following equation: $\text{Ln}[\text{FPG}(\text{mg/dl}) \times \text{TG}(\text{mg/dl})/2]$.¹¹ eGDR was calculated according to the following formula: $\text{eGDR-WC} = 21.16 - (0.09 \times \text{WC}) - (3.41 \times \text{hypertension}) - (0.55 \times \text{A1C})$ or $\text{eGDR-WHR} = 24.31 - (12.22 \times \text{WHR}) - (3.29 \times \text{hypertension}) - (0.57 \times \text{A1C})$ or $\text{eGDR-BMI} = 19.02 - (0.22 \times \text{BMI}) - (3.26 \times \text{hypertension}) - (0.61 \times \text{A1C})$ [hypertension (yes = 1/no = 0), A1C = A1C in %].¹²

Statistical analysis

Descriptive statistics for the categorical variables were assessed using the χ^2 test or Fisher's exact test as appropriate, and for the continuous variables, either an independent t-test or Wilcoxon signed-ranks test was employed when applicable. The Shapiro-Wilk test was used to assess normality. Data for continuous variables with skewed distribution was expressed as median (interquartile range). Various IR surrogate markers were stratified into quartiles and logistic regression analysis was used to determine the association between various surrogate markers with insulin resistance status. The associations between each IR surrogate marker and the presence of insulin resistance status were determined using Spearman's rank correlation coefficients or Pearson's correlation, depending on the type of relationship. Based on a previous study addressing confounders²¹ and general knowledge, we created 3 models: model 1 was unadjusted, model 2 included adjustment for age and sex, and model 3 was adjusted for age, sex, smoking status, the duration of diabetes and the use of metformin, insulin, thiazolidinedione, and statins for the multivariate model. Finally, we performed subgroup analysis in participants with CAD to evaluate the association between the TyG index and eGDR formulas in identifying participants with multi-vessel disease.

A *p*-value of <0.05 was considered statistically significant. All analyses were conducted using the SPSS Statistical Package, version 20 (IBM Corp., Armonk, NY, USA).

RESULTS

Baseline characteristics of the patients

A total of 97 Thai adults with T2D (36.1% female, mean age 61.7 ± 12.0 years, median duration of diabetes 16 years, BMI 26.4 ± 3.7 kg/m², A1C $6.9 \pm 1.2\%$ were enrolled as shown in Figure 1. The mean HOMA-IR in all participants was 3.8 ± 3.0 and the prevalence of IR estimated by HOMA-IR method was 71.1%. Participants with IR (mean HOMA-IR at 4.7) showed younger age and were more obese than those with no IR (mean HOMA-IR at 1.4) as revealed in Table 1. Regarding waist-related anthropometric measures, WC and WHtR were found to be statistically significantly higher than those with no IR, while WHR was not. The mean value of the TyG index also showed statistically significant differences between groups. However, only eGDR calculated by WC and eGDR calculated by WHR showed lower values in participants with IR, whereas eGDR calculated by BMI did not.

Relationship between various IR surrogate markers for identifying IR

All waist-related anthropometric measures and TyG index were positively associated with the HOMA-IR but various eGDR formulas were negatively associated with the HOMA-IR. Based on correlation analysis, the TyG index yielded the most correlation with the presence of IR (moderately positive correlation at $r = 0.49$). eGDR calculated by WC, WHR, and BMI showed poor correlation with the HOMA-IR ($r = 0.25, 0.12, \text{ and } 0.23$ respectively), as shown in the correlation heatmap in Figure 2.

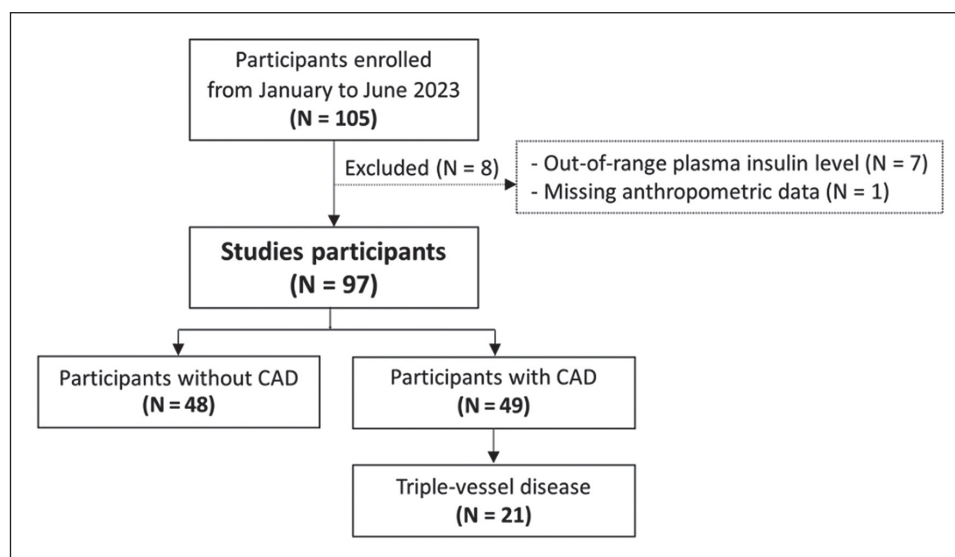


Figure 1. Flow diagram of studied patients (N=97).

The odds ratio for the presence of IR according to each quartile of the TyG index and eGDR formula

Table 2 shows the results of logistic regression of the TyG index and eGDR formula in which model 1 shows unadjusted values whereas models 2 and 3 show values derived after adjusting for potential confounders for the

multivariate model. The highest quartile of the TyG index (>9.22) showed an odds ratio for the presence of IR in all models of more than 10 times higher when compared with the lowest quartile of the TyG index (<8.47). Only the lowest quartile of eGDR calculated by WC (<5.37) was statistically significant in all models when compared with the highest quartile of eGDR calculated by WC (>8.73).

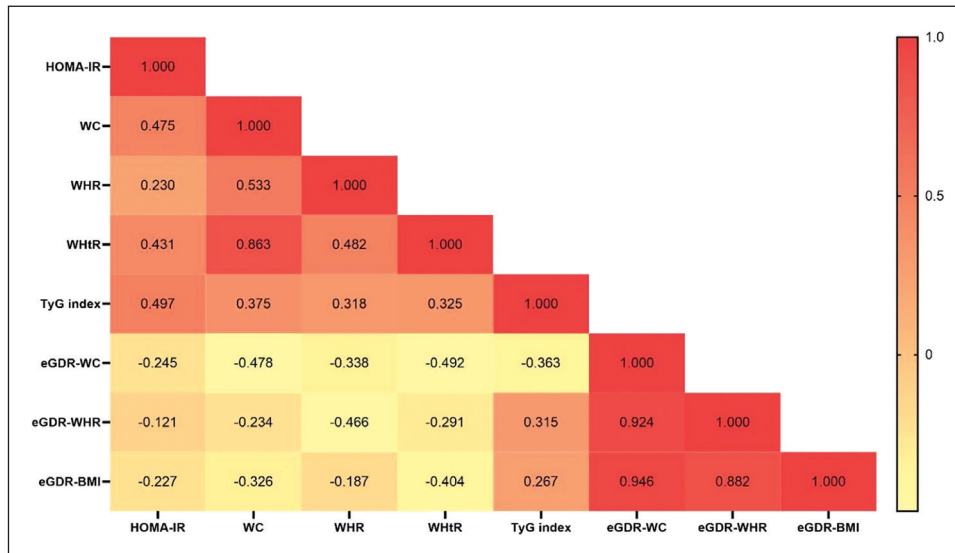


Figure 2. Correlations between HOMA-IR and various insulin indices.

Table 1. Clinical characteristics and laboratory data of studied participants (N = 97)

	Total participants (N = 97)	Participants with HOMA-IR <2.0 (N = 28)	Participants with HOMA-IR ≥2.0 (N = 69)	P-value
Age (yrs)	61.7 ± 12.0	64.2 ± 11.3	60.7 ± 12.2	0.193 ^a
Female (%)	36.1	42.9	33.3	0.376 ^b
Duration of DM (yrs)	16.0 (5.5,25.0)	16.5 (13.2,33.0)	15.0 (5.0,23.0)	0.624 ^c
BMI (kg/m ²)	26.3 (23.4,28.7)	24.0 (22.7,27.6)	26.4 (24.1,29.6)	0.007 ^c
Waist circumference (WC) (cm)	94.0 (86.5-99.5)	90.0 (84.0,94.0)	95.0 (89.0,102.0)	0.002 ^c
Hip circumference (HC) (cm)	98.0 (92.5-105.0)	96.0 (90.0,99.0)	99.0 (95.5,105.5)	0.008 ^c
Waist-to-hip ratio (WHR)	0.95 ± 0.06	0.94 ± 0.05	0.96 ± 0.06	0.126 ^a
Waist-to-height ratio (WHtR)	0.56 (0.52,0.61)	0.54 (0.51,0.58)	0.57 (0.54,0.62)	0.024 ^c
Smoking (%)	16.5	21.4	14.5	0.404 ^d
Presence of hypertension (%)	63.9	64.3	63.8	0.962 ^b
Diabetic retinopathy (%)	28.9	35.7	26.1	0.343 ^b
Diabetic kidney disease (%)	27.8	39.3	23.2	0.109 ^b
Diabetic neuropathy (%)	20.6	32.1	15.9	0.074 ^b
Coronary artery disease (%)	50.5	60.7	46.4	0.201 ^b
Triple-vessel disease (%)	42.9	41.2	43.8	0.862 ^b
Insulin usage (%)	24.7	21.4	26.1	0.630 ^b
Fasting plasma glucose (mg/dL)	124 (109,146)	112.5 (105.8,139.5)	126 (112,148)	0.052 ^c
Total cholesterol (mg/dL)	148 ± 29	149 ± 38	148 ± 24	0.851 ^a
Fasting plasma triglyceride (mg/dL)	112 (83,148)	88.5 (64.8,111.5)	122 (91,169)	<0.001 ^c
Plasma HDL (mg/dL)	56 ± 13	60 ± 11	55 ± 14	0.086 ^a
Plasma LDL (mg/dL)	76 (63,91)	77 (58,90)	76 (64,96)	0.720 ^c
A1C (%)	6.8 (6.2-7.5)	6.5 (5.5,7.1)	6.9 (6.4,7.6)	0.029 ^c
Fasting plasma insulin (mg/dL)	9.4 (5.6-15.5)	4.9 (3.6,5.7)	11.8 (8.9-18.6)	<0.001 ^c
HOMA-IR	2.7 (1.8-4.8)	1.5 (1.1,1.8)	3.7 (2.5,6.0)	<0.001 ^c
Triglyceride-glucose index	8.9 ± 0.5	8.6 ± 0.4	9.0 ± 0.5	<0.001 ^a
Estimated glucose disposal rate (eGDR) calculated by WC	6.6 (5.4,8.7)	7.1 (6.4,8.8)	6.2 (5.0,8.7)	0.019 ^c
Estimated glucose disposal rate (eGDR) calculated by WHR	6.2 (5.1,8.6)	6.4 (5.8,8.8)	6.0 (4.8,8.6)	0.168 ^c
Estimated glucose disposal rate (eGDR) calculated by BMI	6.4 (5.4,8.7)	7.2 (6.4,8.3)	5.9 (5.2,9.1)	0.021 ^c

^a Independent t-test

^b Chi-square test

^c Wilcoxon signed-rank test

^d Fisher's exact test

Continuous data were presented as means ± SD or median (IQR); categorical data were presented as number (%)

Table 2. Multivariate logistic regression of different indices for predicting the presence of insulin resistance (Model 1: unadjusted; Model 2: adjusted for age and sex; Model 3: adjusted for age, sex, duration of diabetes, smoking, the usage of insulin, metformin, thiazolidinedione and statin for the multivariate model)

Parameter	Model 1, OR (95%CI)	p-value	Model 2, OR (95%CI)	p-value	Model 3, OR (95%CI)	p-value
WC						
Q1; <86.5	Reference		Reference		Reference	
Q2; 86.5-93.9	2.00 (0.62-6.42)	0.244	1.84 (0.56-6.09)	0.315	1.05 (0.25-4.53)	0.944
Q3; 94.0-99.5	4.00 (1.13-14.18)	0.032	4.67 (1.26-17.25)	0.021	6.68 (1.23-36.41)	0.028
Q4; >99.5	7.00 (1.64-29.85)	0.009	6.81 (1.57-29.60)	0.011	5.76 (1.20-27.64)	0.029
WHR						
Q1; <0.91	Reference		Reference		Reference	
Q2; 0.91-0.95	2.40 (0.67-8.65)	0.181	1.99 (0.52-7.43)	0.306	1.73 (0.42-7.22)	0.451
Q3; 0.96-0.98	1.00 (0.31-3.22)	1.000	0.83 (0.24-2.89)	0.772	0.71 (0.18-2.76)	0.617
Q4; >0.98	2.28 (0.63-8.25)	0.209	2.18 (0.59-8.07)	0.243	1.92 (0.48-7.72)	0.357
WHtR						
Q1; <0.52	Reference		Reference		Reference	
Q2; 0.52-0.56	1.73 (0.54-5.53)	0.355	2.49 (0.71-8.76)	0.156	2.87 (0.69-11.8)	0.145
Q3; 0.57-0.61	6.77 (1.61-28.54)	0.009	11.37 (2.35-54.9)	0.002	9.98 (1.84-54.17)	0.008
Q4; >0.61	3.51 (0.99-12.35)	0.051	6.85 (1.57-29.9)	0.011	5.40 (1.14-25.58)	0.033
TyG index						
Q1; <8.47	Reference		Reference		Reference	
Q2; 8.47-8.90	2.13 (0.67-6.78)	0.203	2.74 (0.80-9.53)	0.108	5.84 (1.26-27.14)	0.024
Q3; 8.91-9.22	3.00 (0.88-10.18)	0.078	3.42 (0.97-12.05)	0.056	5.87 (1.29-26.62)	0.022
Q4; >9.22	11.00 (2.10-57.50)	0.004	11.7 (2.19-62.26)	0.004	19.80 (2.82-139.13)	0.003
eGDR-WC						
Q1; <5.37	9.47 (1.06-84.37)	0.044	15.11 (1.58-144.66)	0.018	31.68 (1.95-513.54)	0.015
Q2; 5.37-6.62	1.06 (0.31-3.66)	0.928	1.82 (0.45-7.28)	0.399	1.92 (0.39-9.50)	0.423
Q3; 6.63-8.73	0.35 (0.11-1.15)	0.083	0.40 (0.12-1.40)	0.152	0.37 (0.07-1.75)	0.209
Q4; >8.73	Reference		Reference		Reference	
eGDR-WHR						
Q1; <5.14	2.88 (0.65-12.87)	0.165	4.74 (0.94-23.94)	0.059	7.55 (1.11-51.27)	0.039
Q2; 5.14-6.22	0.73 (0.22-2.43)	0.611	1.07 (0.29-3.91)	0.916	1.05 (0.24-4.64)	0.947
Q3; 6.23-8.61	0.69 (0.21-2.29)	0.541	0.85 (0.24-2.99)	0.803	0.92 (0.23-3.62)	0.902
Q4; >8.61	Reference		Reference		Reference	
eGDR-BMI						
Q1; <5.37	6.05 (0.65-56.37)	0.114	7.58 (0.78-73.82)	0.081	13.02 (0.71-238.92)	0.084
Q2; 5.37-6.44	0.68 (0.19-2.52)	0.561	0.96 (0.23-4.08)	0.961	0.62 (0.11-3.49)	0.583
Q3; 6.45-8.70	0.16 (0.04-0.57)	0.005	0.20 (0.05-0.75)	0.017	0.11 (0.02-0.58)	0.009
Q4; >8.70	Reference		Reference		Reference	

OR = Odds Ratio, CI = Confidence Interval

ROC analysis using the TyG index and eGDR calculated by WC for identifying IR

The results of ROC analysis using the TyG index and eGDR calculated by WC for identifying IR are shown in Figure 3. The optimal cut-off values, using Youden's index for the TyG index and eGDR calculated by WC were 9.04 (sensitivity 50.7%, specificity 60.5%) and 6.59 (sensitivity 59.4%, specificity 75.0%), respectively.

Performance of TyG and eGDR formulas in predicting the severity of CAD among T2D with CAD

A total of 49 T2D with CAD (20.4% female, mean age 67.5±9.4 years, median duration of diabetes 23 years, BMI 25.8±4.1 kg/m², A1C 7.1±1.4%) were analyzed in the subgroup of this cohort. Triple-vessel disease (TVD) was found in 42.8% of these participants as revealed in Table 3. Among T2D with CAD group, the TyG index was found to have no significant correlation with the presence of triple-vessel disease ($r = 0.08$, $p = 0.57$). Only eGDR calculated by WC and BMI showed a significant moderate correlation with triple-vessel disease ($r = -0.34$, -0.33 respectively).

DISCUSSION

In the present cross-sectional study, we confirmed that the TyG index was the reliable surrogate marker for IR among Thai people with T2D. Measures of plasma lipid concentrations are readily available in routine clinical practice and standardized to a much greater degree than assays of fasting plasma insulin concentration. Additionally, besides being a marker associated with IR, the TyG index is also a valid marker for risk stratification of participants with T2D.²²⁻²⁴ Although measures of IR have not yet been integrated into clinical guidelines, several studies have confirmed the clinical significance of IR beyond glycemic control alone in people with T2D.¹⁻³ Therefore, the presence of IR should also be considered as one of the targets for improving diabetes management.

Obesity alone does not adequately reflect the different obesity phenotypes as the distribution of adiposity is also important.³ There is an accumulating body of evidence that gluteofemoral adipose tissue may even be protective.²⁵ In our study, waist-related anthropometric measures correlated positively with the HOMA-IR but their predictive

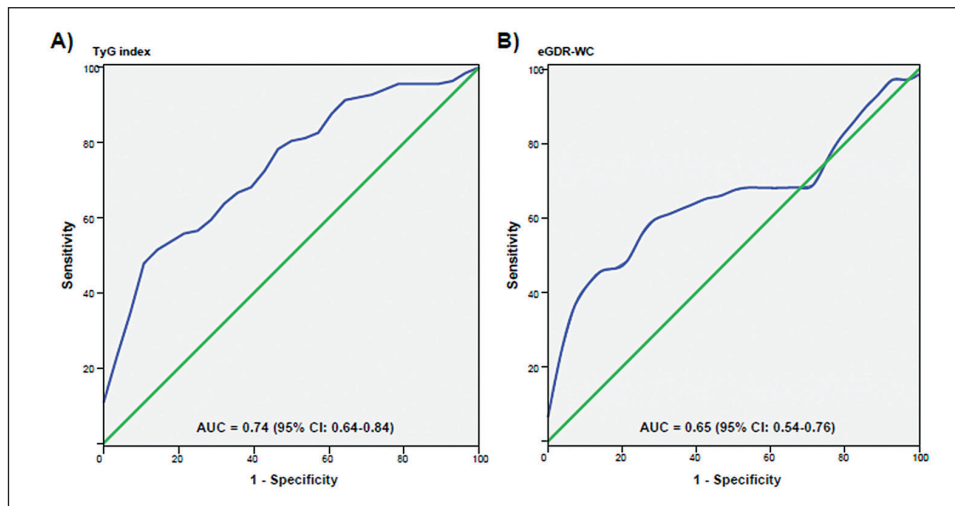


Figure 3. Receiver operating characteristic analysis for predicting the presence of insulin resistance defined by the HOMA-IR from (A) TyG index and (B) eGDR calculated by waist circumference.

Table 3. Clinical characteristics and laboratory data of studied participants with CAD (N = 49)

	Total participants (N =49)	Participants with triple-vessel disease (N = 21)	Participants without triple-vessel disease (N = 28)	P-value
Age (yrs)	67.5±9.4	67.5±10.0	67.6±9.0	0.972 ^a
Female (%)	20.4	19.0	21.4	0.565 ^d
Duration of DM (yrs)	22.9±12.2	23.9±11.0	22.2±13.2	0.638 ^a
BMI (kg/m ²)	24.4 (22.9,28.3)	24.0 (22.8,29.8)	24.7 (23.3,26.7)	0.888 ^c
Waist circumference (WC) (cm)	93.0 (86.0,99.5)	95.0 (86.0,110.0)	92.0 (86.0,98.8)	0.384 ^c
Hip circumference (HC) (cm)	96.0 (90.5,104.0)	97.0,90.5,109.0	96.0 (90.3,100.1)	0.110 ^c
Waist-to-hip ratio (WHR)	0.96±0.07	0.96±0.07	0.97±0.07	0.622 ^a
Waist-to-height ratio (WHtR)	0.56 (0.52,0.62)	0.55 (0.52,0.63)	0.56 (0.52,0.59)	0.747 ^c
Smoking (%)	20.4	23.8	17.9	0.609 ^d
Presence of hypertension (%)	83.7	95.2	75.0	0.062 ^d
Diabetic retinopathy (%)	44.9	47.6	42.9	0.740 ^b
Diabetic kidney disease (%)	53.1	42.9	60.7	0.215 ^b
Diabetic neuropathy (%)	34.7	42.9	28.6	0.299 ^b
Insulin usage (%)	38.8	47.6	32.1	0.271 ^b
Fasting plasma glucose (mg/dL)	125 (109,155)	143 (106,170)	124 (110,140)	0.284 ^c
Total cholesterol (mg/dL)	135 (118,153)	132 (114,154)	135 (119,151)	0.801 ^c
Fasting plasma triglyceride (mg/dL)	114 (73,149)	111 (77,138)	115 (65,150)	0.816 ^c
Plasma HDL (mg/dL)	54±12	54±13	54±12	0.982 ^a
Plasma LDL (mg/dL)	67 (52,83)	65 (43,81)	68 (54,84)	0.396 ^c
A1C (%)	6.9 (6.0,7.7)	7.2 (6.0,8.0)	6.8 (6.0,7.5)	0.327 ^c
Fasting plasma insulin (mg/dL)	7.9 (5.2,13.8)	7.0 (4.2,18.0)	8.0 (5.5,11.3)	0.856 ^c
HOMA-IR	2.3 (1.7,4.4)	2.1 (1.5,6.6)	2.3 (1.8,3.7)	0.944 ^c
Triglyceride-glucose index	8.9±0.5	8.9±0.6	8.8±0.5	0.570 ^a
Estimated glucose disposal rate (eGDR) calculated by WC	6.1±1.9	5.4±1.5	6.7±1.9	0.017 ^a
Estimated glucose disposal rate (eGDR) calculated by WHR	6.3±1.8	5.3±1.3	6.1±2.1	0.127 ^a
Estimated glucose disposal rate (eGDR) calculated by BMI	5.8±1.8	5.6±1.5	6.8±1.8	0.020 ^a

^a Independent t-test

^b Chi-square test

^c Wilcoxon signed-rank test

^d Fisher's exact test

Continuous data were presented as means ± SD or median (IQR); categorical data were presented as number (%)

values were inferior to the TyG index. IR is an important risk factor for atherosclerosis and a predictor of adverse cardiovascular events after revascularization in patients with CAD.²⁶ People with diabetes are more likely to have diffuse and multivessel vascular lesions and represent a challenging group of the population of candidates eligible for revascularization techniques.²⁷ Previous studies demonstrated the role of both the TyG index and eGDR as

an indicator of severe CAD in the general population.²⁸⁻³⁰ Several possible explanations for these findings present TG and TG-rich lipoprotein (TGRL) as the main causes of residual ASCVD despite statin use.³¹ Elevated plasma TG serves as a marker for TGRL and their remnants which up-regulate inflammation, oxidative stress, and foam cell formation in vascular endothelial cells and macrophages.³² Therefore, elevated plasma TG is associated with the activating process

of atherosclerosis even in patients with low LDL-C levels. Our present study showed that only eGDR-WC and eGDR-BMI demonstrated a significant correlation with triple vessel disease among subgroup analysis in individuals with T2D and CAD. It might be explained by the parameters of glycemic status (A1C results) and the presence of hypertension which were both incorporated in the eGFR formula and could be more predictive of the severity of atherosclerosis than the single time point determination of plasma glucose and triglyceride within the TyG index. Future studies should be performed to define the role of the eGDR formula in predicting the burden of atherosclerosis.

The phenotype of T2D in Asians is characterized by young age at the time of onset, predisposition to beta-cell failure, and visceral adiposity even if they do not reach the BMI cut-offs for overweight or obesity in non-Asian populations.³³ Clinical markers that improve the earlier detection of IR would allow the targeting of intensive treatments with lifestyle changes and early uses of insulin-sensitizing medications to those most likely to benefit. Even in an Asian population, there is heterogeneity in the pathogenesis of DM and risks for complications between ethnic/racial groups. In contrast to the South Asian population, lean Thai people with T2D have insulin secretion as a primary defect as stated in a previous euglycemic clamp study done in people with newly diagnosed T2D.³⁴ The presence of IR received little attention in people with a long-standing duration of T2D. Increased IR was noted not only in people with increased adiposity, hypertension, and dyslipidemia, but also in people with frailty.⁷ Additional validated cohorts in the Southeast Asian population with long-standing DM should be conducted to clarify the roles of both the TyG index and eGDR as risk enhancers for reclassifying the risk of individual patients.

Several limitations could have influenced our results. First, the limitations related to the cross-sectional nature of this study and the limited sample size from a specialized diabetes center in Thailand should be considered. The causal relationship between various simple insulin indices and clinical outcomes needs to be confirmed in future prospective studies. Second, the possibility of residual confounding factors cannot be completely ruled out which could affect our results. Other confounding factors like socioeconomic status, physical inactivity, family history, frailty, inflammatory diseases, and environmental exposure were not considered in our study. Third, the cut-off values for HOMA-IR varied greatly from 2.0 to 3.6 in several previous studies based on different geographical populations and studied cohorts.³⁵⁻³⁷ However, our study confirmed the significant association between the TyG index and eGDR with the concept of HOMA-IR as reported in previous studies.^{12,13} There are no standardized diagnostic criteria or methods to define IR from the HOMA-IR and the defined criteria depend on factors such as age, sex, ethnicity, and clinical conditions.³⁸ It should be interpreted with caution when extrapolating our findings to other populations. Finally, the limitation of HOMA-IR in participants who

were on insulin should be acknowledged. Exogenous insulin might interfere with endogenous insulin secreted into the portal circulation. However, it is still possible to use HOMA-IR to assess insulin sensitivity in subjects treated with insulin as previously mentioned.³⁹

CONCLUSION

The TyG index was a useful simple marker for identifying the presence of IR in Thai people with T2D. While the TyG index integrated only fasting glucose and triglyceride levels, eGDR combined other IR factors. Our study demonstrated that the TyG index demonstrated more predictive utility in identifying IR than eGDR. Future longitudinal studies are warranted to demonstrate the potential prediction value of cardiovascular morbidity and mortality for these markers.

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Statement of Authorship

All authors are certified in fulfillment of ICMJE authorship criteria.

CRedit Author Statement

WC: Conceptualization, Software, Formal analysis, Data Curation, Visualization; **YT:** Methodology, Validation, Investigation, Writing – original draft preparation; **SN:** Resources, Project administration; **EW:** Writing – review and editing; **SK:** Writing – review and editing; **TH:** Supervision, Funding acquisition

Data Availability Statement

Datasets analyzed in the study are under license and not publicly available for sharing.

Author Disclosure

The authors declared no conflict of interest.

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