ORIGINAL

Triglyceride glucose index is superior biomarker for predicting type 2 diabetes mellitus in children and adolescents

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Abstract. The triglyceride-glucose (TyG) index is associated with predicting type 2 diabetes mellitus (T2DM), but its relationship with homeostatic model assessment of insulin resistance (HOMA-IR) in T2DM is not established. We aimed to investigate the role of TyG index for detection of T2DM in children and adolescents and compare it with HOMA-IR. A cross sectional study was performed in 176 overweight or obese children and adolescents with mean age of 11.34 ± 3.24 years. TyG index was calculated as ln (fasting triglyceride (TG) [mg/dL] × fasting glucose [mg/dL]/2). Of a total of 176 subjects, 57 (32%) were diagnosed with T2DM. Significant differences were observed in the TyG index between T2DM and non-T2DM ($p < 0.001$). The TyG index had a positive correlation with fasting glucose ($r = 0.519$, $p < 0.001$), HOMA-IR ($r = 0.189$, $p < 0.017$), HbA1c ($r = 0.429$, $p < 0.001$), total cholesterol (TC) ($r = 0.257$, $p = 0.001$), TG ($r = 0.759$, $p < 0.001$), and low-density lipoprotein cholesterol (LDL-C)($r = 0.152$, $p < 0.001$), and a negative correlation with high-density lipoprotein cholesterol (HDL-C)($r = -0.107$, $p < 0.001$) after controlling for sex, age and BMI standard deviation scores (SDS). In multiple regression analyses, 91.8% of the variance in TyG index was explained by age, glucose, HOMA-IR, TG, LDL-C, and HDL-C ($p < 0.001$). In the receiver operating characteristic (ROC) analysis, the TyG index [area under the curve (AUC) 0.839)] showed a better performance compared to HOMA-IR (AUC 0.645) in identifying patients with T2DM ($p < 0.001$). In conclusion, the TyG index had significant association with insulin resistance in T2DM and was superior to HOMA-IR in predicting T2DM in children and adolescents.

Key words: Triglyceride glucose index, Insulin resistance, Type 2 diabetes mellitus, Surrogate marker

THE PREVALENCE of T2DM in children and adolescents is increasing in many countries, including South Korea [1-5]. The main pathophysiologic mechanism of T2DM is insulin resistance (IR), and many surrogate markers of IR have been suggested [6, 7]. The HOMA-IR using fasting insulin and glucose is useful for detection of IR related disease such as T2DM, metabolic syndrome (MetS), cardiovascular diseases (CVD), and nonalcoholic fatty liver disease (NAFLD), and has been widely used in clinical practice [8-11]. The TyG index calculated as ln(fasting TG [mg/dL] × fasting glucose [mg/dL]/2) is emerging as a reliable and simple surrogate marker of IR [12]. The TyG index has been known to excellent marker for detection of T2DM, MetS, CVD, and NAFLD [13-16].

In general, the use of a serum insulin test is limited because of its high cost and narrow indications, whereas the TyG index is in the spotlight as a widely used IR surrogate marker because these limitations are relatively small. Currently, it is reported that the TyG index can detect IR-related diseases even better than HOMA-IR [14, 16]. In adults, the TyG index has been reported to be useful in detecting the development of T2DM and evaluating glycemic control in T2DM patients [17]. Although the TyG index is useful for detection of T2DM, the mechanism associated with T2DM has not yet been clearly identified. Determining the relationship between the TyG index and HOMA-IR is necessary to understand the role of the TyG index in T2DM. However, there are few studies on the role of the TyG index in children and adolescents with T2DM, and the relationship between the TyG index and HOMA-IR in T2DM is rare even in adults.

Therefore, the purpose of this study is to explore the role of the TyG index in the detection of development of

T2DM in children and adolescents. We aimed to evaluate the relationship between the TyG index and HOMA-IR and to compare the ability between the TyG index and HOMA-IR in T2DM detection.

Subjects and Methods

Subjects

This study is a cross sectional study analyzing clinical data from subjects evaluated insulin resistance at the pediatric endocrine clinic between January 2010 and July 2020. A total of 176 overweight and obese children and adolescents with mean age of 11.34 ± 3.24 years had complete data for fasting test of glucose, TC, HDL-C, TG, HbA1c, and insulin.

Children and adolescents who were treated for any endocrine abnormalities, such as diabetes mellitus, dyslipidemia, hypertension, non-alcoholic fatty liver disease, thyroid disease, and growth hormone deficiency, were excluded. Overweight subjects were defined as those having a body mass index (BMI) at or above the 85th percentile and below the 95th percentile for children and adolescents of the same sex and age. Obesity was defined as a BMI at or above the 95th percentile for children and adolescents of the same sex and age. T2DM was diagnosed according to the American Diabetes Association criteria by 2-h glucose levels ≥200 mg/dL during an OGTT, fasting serum glucose 126mg/dL, or HbA1c 6.5%. Subjects with T2DM were educated on lifestyle modification and prescribed treatment with metformin. Subjects with ketoacidosis or HbA1c >8.5% were treated with a combination of metformin and long-acting insulin according to the clinical practice consensus guidelines of the International Society for Childhood and Adolescent Diabetes [18]. None of the participants had diabetic ketoacidosis. Genetic testing was not performed since the participants did not have clinical characteristics of diabetes mellitus due to a genetic disease, such as genetic defects in mitochondrial DNA or maturity onset diabetes. The present study was approved by the Institutional Review Board of Hallym University Kangdong Sacred Heart Hospital (IRB No. 2021-01-006).

Measurements

Height was measured to the nearest 0.1 cm using a Harpenden stadiometer (Holtain Ltd., Crymych, Wales, UK), and weight was measured to the nearest 0.1 kg using a digital scale. The BMI was calculated by dividing the weight by the height squared (kg/m^2). The SDS for height, weight, and BMI were calculated based on the 2007 Korean National Growth Charts by using the LMS (L, lambda for the Box-Cox power for skewness; M, mu

for the median; S, sigma for the generalized coefficient of variation) method (SDS = [measured value/M]$^{1/L}$/LS) [19].

Blood samples were obtained from the antecubital vein after participants had overnight fasting for at least 10 hours. Biochemistry tests, including tests of glucose, TC, HDL-C, TG, HbA1c, and insulin levels, were performed using an automatic analyzer (Hitachi 747, Hitachi, Tokyo, Japan). The LDL-C level (mg/dL) was calculated using Friedewald's equation [20]. The TyG index was calculated as follows: ln(fasting TG [mg/dL] × fasting glucose [mg/dL]/2) [21], and HOMA-IR was calculated with (fasting insulin [mIU/L] x fasting glucose [mg/dL]/405) [22].

Statistical analysis

Statistical analysis was performed using statistical package for the social sciences (SPSS) version 26.0 (IBM Co., Armonk, NY, USA) and MedCalc version 16.8.4 (MedCalc Software, Ostend, Belgium). To determine statistical significance between groups, Mann-Whitney *U* test was used for continuous variables and categorical variables. The unadjusted and adjusted Pearson's correlation tests were performed to examine the correlation between the TyG index and clinical parameters in T2DM. We used two models to adjust for confounders: model 1 was adjusted for sex and age; model 2 was adjusted for sex, age, and BMI SDS. A multiple linear regression analysis was conducted to investigate the association between TyG index and and clinical parameters in T2DM. ROC curve was used to discriminate the ability of IR surrogate markers to detect development of T2DM, which were used to compare the ability of the TyG index to the HOMA-IR. Continuous variables and clinical variables are reported as means ± standard deviations. Statistical significance was defined as a *p*-value <0.05.

Results

Clinical characteristics of the study population

The comparison of the clinical characteristic and biochemistry parameters of the study subjects, with and without T2DM, is presented in Table 1. Of a total of 176 subjects, 122 (69.3%) were non-T2DM, and 54 (30.7%) were T2DM. The mean age of non-T2DM and T2DM was 9.92 ± 2.56 and 14.25 ± 2.29 years, respectively. Height SDS (*p* = 0.016), glucose (*p* < 0.001), HbA1c (*p* < 0.001), HOMA-IR (*p* = 0.001), and TyG index (*p* < 0.001) were higher in T2DM than in non-T2DM, whereas weight SDS (*p* = 0.414), BMI SDS (*p* = 0.001), and HDL-C (*p* = 0.013) were decreased in subjects with T2DM. Insulin was lower in T2DM than non-T2DM, but there was no statistical significance.

Table 1 Clinical characteristics of study population (n = 176)

	Non-T2DM n = 122	T2DM n = 54	p
Age (years)	9.92 ± 2.56	14.25 ± 2.29	<0.001
Height SDS	0.99 ± 1.17	1.49 ± 1.39	0.016
Weight SDS	2.60 ± 0.84	2.42 ± 1.51	0.414
BMI SDS (kg/m²)	3.01 ± 0.93	2.19 ± 1.63	0.001
TC (mg/dL)	179.51 ± 31.46	181.63 ± 44.22	0.718
HDL-C (mg/dL)	48.43 ± 10.10	44.15 ± 10.86	0.013
TG (mg/dL)	130.90 ± 90.30	147.80 ± 79.50	0.237
LDL-C (mg/dL)	112.37 ± 25.00	115.19 ± 32.30	0.477
Glucose (mg/dL)	93.60 ± 10.18	195.44 ± 83.72	<0.001
Insulin (μU/mL)	18.66 ± 14.04	17.38 ± 15.20	0.586
HbA1c (%)	5.41 ± 0.38	9.92 ± 2.63	<0.001
HOMA-IR	4.44 ± 3.57	7.30 ± 5.64	0.001
TyG index	8.56 ± 0.55	9.36 ± 0.64	<0.001

SDS, standard deviation score; BMI, body mass index; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol, LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; TyG index, triglyceride and glucose index; HOMA-IR, homeostatic model assessment of insulin resistance

Correlation between TyG index and clinical parameters

Unadjusted Pearson's correlation analysis indicated that age (r = 0.487, p < 0.001), TC (r = 0.245, p = 0.001), HDL-C (r = –0.447, p < 0.001), TG (r = 0.740, p < 0.001), LDL-C (r = 0.278, p < 0.001), HbA1c (r = 0.590, p < 0.001), glucose (r = 0.632, p < 0.001), and HOMA-IR (r = 0.338, p < 0.001) were statistically correlation with T2DM. Adjusted Pearson's correlation analysis showed that these trends were more remarkable after adjustment for sex and age (adjusted model 1), or sex, age, and BMI SDS (adjusted model 2) (Table 2).

Association between TyG index and clinical parameters

In multiple linear regression analyses (Table 3), with TyG index as the dependent variable and sex, age, BMI SDS, glucose, TC, TG, LDL-C, HDL-C, insulin, and HOMA-IR as the independent variables, 91.9% of the variance in TyG index was explained by age (β = 0.057, P = 0.036), FSG (β = 0.530, p < 0.001), TG (β = 0.617, p < 0.001), LDL-C (β = 0.150, p < 0.001), HDL-C (β = –0.104, p < 0.001), and HOMA-IR (β = 0.053, p = 0.029).

Comparison of ROC curves between the TyG index and HOMA-IR

The AUC for TyG index and HOMA-IR was 0.839 (95%CI 0.776–0.889, p < 0.001) and 0.645 (95%CI 0.570–0.716, p < 0.001), respectively (Fig. 1). In the pairwise comparison of ROC curves, the TyG index showed a better performance in comparison HOMA-IR in detection of development of T2DM (difference between areas 0.193, 95% CI 0.096–0.291, p < 0.001).

Discussion

The main finding of the present study was that the TyG index proved to be valuable in the detection of T2DM, and was associated with HOMA-IR, showing that the TyG index has a role of surrogate measure of IR in children and adolescents with T2DM. Furthermore, the TyG index was superior to HOMA-IR for detection of development of T2DM.

In the period of children and adolescents, it is difficult to present normal reference range for IR and to suggest cutoff values for IR related diseases due to the physiological changes that temporarily increase during puberty and the differences according to sex and age [10, 23]. Hyperinsulinemic euglycemic clamp (HEIC) is limited in clinical use because of invasive and time-consuming, therefore HOMA-IR is widely used as a surrogate marker for IR [7, 24]. HOMA-IR can be used as a useful indicator for assessing IR and metabolic risk children and adolescents [8, 9]. Nevertheless, there are several limitations using HOMA-IR to evaluate IR related

Table 2 Unadjusted and adjusted correlations between TyG index and clinical parameters in type 2 diabetes mellitus (*n* = 176)

	Unadjusted model		Adjusted model 1		Adjusted model 2	
	r	*p*	*r*	*p*	*r*	*p*
Sex (girls)	–0.058	0.441	—	—	—	—
Age (years)	0.487	<0.001	—	—	—	—
BMI SDS (kg/m²)	–0.134	0.076	0.004	0.958	—	—
TC (mg/dL)	0.245	0.001	0.271	0.001	0.272	<0.001
HDL-C (mg/dL)	–0.447	<0.001	–0.369	<0.001	–0.370	<0.001
TG (mg/dL)	0.740	<0.001	0.753	<0.001	0.756	<0.001
LDL-C (mg/dL)	0.278	<0.001	0.289	<0.001	0.289	<0.001
HbA1c (%)	0.590	<0.001	0.412	<0.001	0.425	<0.001
Insulin (μU/mL)	0.111	0.144	0.028	0.720	0.029	0.716
FSG	0.632	<0.001	0.509	<0.001	0.518	<0.001
HOMA-IR	0.338	<0.001	0.209	0.007	0.220	0.005

SDS, standard deviation score; BMI, body mass index; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; FSG, Fasting serum glucose; TyG index, triglyceride and glucose index; HOMA-IR, homeostatic model assessment of insulin resistance
The adjusted model 1 was performed after controlling for sex and age.
The adjusted model 2 was performed after controlling for sex, age, and BMI SDS.

diseases in children and adolescents. In children and adolescents, it is difficult to interpret HOMA-IR in consideration of the effects of sex, age, BMI SDS, and pubertal period, therefore a normal reference has not yet been presented [7, 25-28]. Consequently, the HOMA-IR cannot be used to evaluate treatment response. Also, the indications for insulin test are narrow and costly, and the insulin test method is not standardized [7]. Oral glucose tolerance test can be considered to discriminate whether normal glucose tolerance or impaired glucose tolerance, but repeated tests are recommended due to poor reproducibility, and are practically difficult to perform for children and adolescents in clinics [29].

In 2008, Simental-Mendia L. E. *et al.* proposed that TyG index using fasting glucose and fasting triglycerides could be useful as insulin resistance surrogate marker [21]. According to a hyperglycemic clamp validated study, TyG index presented IR by a moderated degree of agreement with hyperglycemic clamp and performs better than HOMA [30]. Recent studies report that the TyG index is excellent for detecting IR-related diseases. The TyG index can perform as better surrogate marker for diagnosing MetS [14]. The TyG index has been shown to be useful presented in detection of development of MetS in population-based studies of different races. Depending on races and definitions of MetS criteria, TyG index cutoff values of 8.45–8.65 in Mexican American, 8.15–8.35 in Non-Hispanic Black, and 8.38–8.66 in Korean were suggested [31, 32]. For prediction

Table 3 Association between TyG index and clinical parameters in T2DM using multiple linear regression analysis in the study population (*n* = 176)

Variables	Multivariate (adjusted R^2 0.919, $p < 0.001$)	
	Standarized *β*	*p*
Age (years)	0.057	0.036
Glucose (mg/dL)	0.530	<0.001
TG (mg/dL)	0.617	<0.001
LDL-C (mg/dL)	0.150	<0.001
HDL-C (mg/dL)	–0.104	<0.001
HOMA-IR	0.053	0.029

TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance

of NAFLD, the TyG index was also useful and superior to HOMA-IR [16]. Recently, several studies have reported the useful of the TyG index for prediction of cardiovascular disease in adults [15, 33].

In adults, the TyG index has been reported as a potential predictor of prediabetes and T2DM and useful tool for assessment of long term glycemic in T2DM [13, 17, 34]. However, most studies have been done in adults, and studies in children and adolescents are rare. In children and adolescents, Mohd Nor, N.S *et al.* compared HIEC and TyG index in children and adolescents and reported that TyG index can be usefully used as a
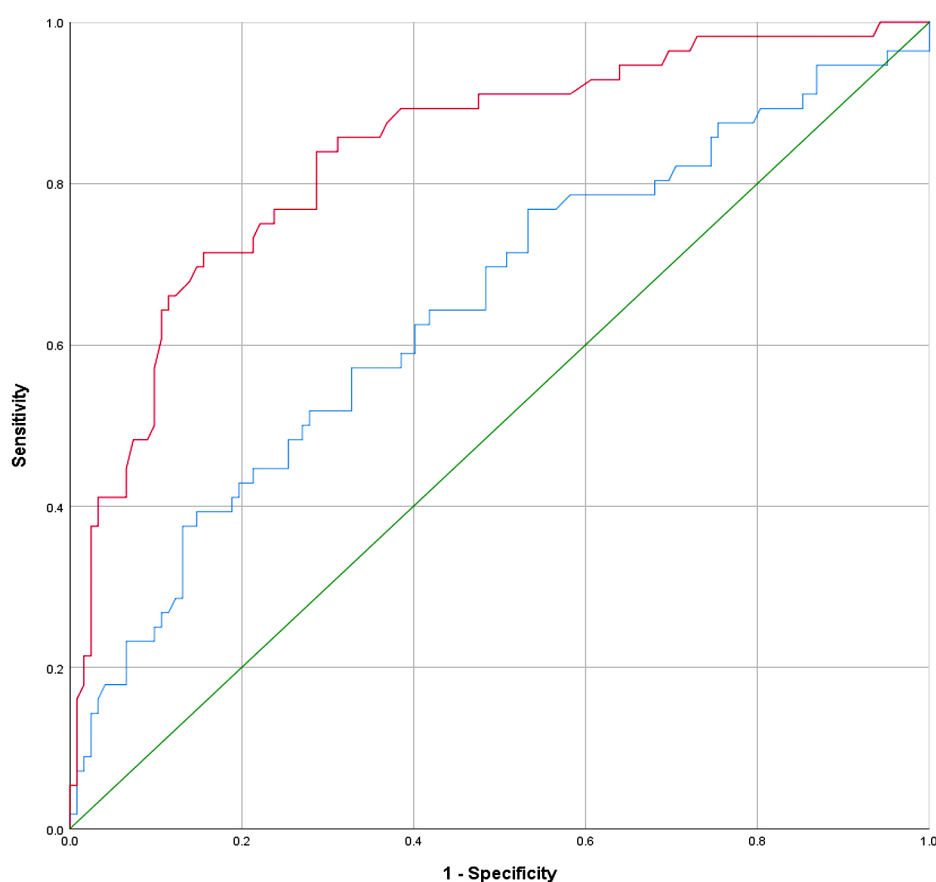
Fig. 1 ROC curves comparison of AUC for the TyG index (red line) and HOMA-IR (blue line) for detection T2DM

surrogate marker of IR in T2DM [12]. Low S. *et al.* reported that the TyG index is useful for the detection of development of T2DM in adults and suggested that a future study for the relationship between the TyG index and HOMA-IR is necessary to further clarify the role of the TyG index [13]. Since there are few studies comparing TyG index and HOMA-IR in T2DM, we performed a study comparing the TyG index and HOMA-IR to further clarify the role of TyG index in T2DM.

IR exists when insulin levels are higher than expected relative to the level of glucose. In general, elevations in basal insulin levels are common in patients with IR associated with T2DM [35]. HOMA-IR, which reflects hyperglycemia and hyperinsulinemia, can be assumed to be more useful than the TyG index in the detection of T2DM. However, the results of this study showed that the TyG index was statistically useful in diagnosing T2DM better than HOMA-IR. This result is presumed to be influenced by impaired insulin secretion due to decreased β-cell dysfunction, which is characteristic of T2DM. The function of β-cell is diminished in patients with T2DM. β-cell function begins to decrease from the onset of hyperglycemia, decreases by –80% in IGT patients and further decreases in T2DM patients [36].

Subjects in this study had a statistically significantly lower BMI-SDS in the T2DM group than in the non-T2DM group, and the insulin secretion was also low, although there was no statistically significant difference. This suggests that subjects with T2DM in this study may have had prolonged hyperglycemia. Therefore, we conclude that the association between persistence of hyperglycemia and decreased β-cell function influences the role of HOMA-IR for assessing IR. This limitation eventually suggests that HOMA-IR may be less useful in assessing IR in T2DM compared to the TyG index.

The role of the TyG index in the mechanism by which T2DM occurs is not yet clear, but it can be explained as follows: In obesity, free fatty acids are elevated due to expansion of adipose tissue mass. Excess fatty acids, accompanied by accumulation of TG in pancreatic β-cells, result in chronic cellular dysfunction and damage. This process has come to be termed lipotoxicity and is usually accompanied by TG accumulation. Lipotoxicity has a detrimental effect on glucose homeostasis, which has a synergistic toxic effect in the state of hyperglycemia (glucotoxicity). The glucotoxicity and lipotoxicity conditions induce pancreatic β-cell dysfunction, alters the processes of insulin gene transcription and insulin

secretion and these has been suggested as one of the mechanisms of development of T2DM [37, 38].

This study presented the usefulness of the TyG index in detecting the development of T2DM. Although it was confirmed that the TyG index is superior to HOMA-IR, additional studies on the TyG index are needed in order to be expected to be used in actual clinics. First, it is necessary to study how the TyG index is affected by various confounding factors such as age, gender, BMI, and puberty, like HOMA-IR. Second, it is necessary to confirm whether the distribution of the TyG index has severe fluctuations like HOMA-IR or a stable linear distribution by large-population based studies. Third, it is known that the TyG index have different values for different races, but it is necessary to study whether the TyG index has the same role in detecting the development of T2DM.

The limitations of this study are as follows. First, the effects of pubertal period on the TyG index could not be evaluated due to the lack of information on the Tanner stage of the subjects. Studies on the relationship between the TyG index and puberty have not yet been performed, therefore further studies are needed to be evaluated. Second, since this study was carried out with a retrospective design, it was not possible to additionally compare the TyG index with that of normal BMI, which is a healthy control, so there was a limitation in clarifying the

effect of BMI on the TyG index. However, even among the high-risk groups of T2DM, such as the overweight and obese, the excellent detection ability for the onset of T2DM shows a meaningful result despite these limitations. Third, since this study was designed as a cross-sectional analysis, it was not possible to evaluate the change of the TyG index according to the progression of T2DM, so there was a limitation in clarifying the relationship between T2DM and TyG index more clearly. A study is needed to evaluate the relationship between the TyG index and HOMA-IR according to the progress of T2DM in the future.

In conclusion, our results showed that TyG index has correlation with HOMA-IR and is superior to HOMA-IR for the detection of T2DM. The TyG index may be a potentially simple and useful tool for predicting T2DM in children and adolescents.

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Disclosure

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