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ORIGINAL RESEARCH REPORT

Determining insulin resistance (IR) in obese adolescents using TyG index

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Article Info	ABSTRACT
	Background: Obesity is associated with insulin resistance (IR). Triglyceride glucose (TyG) index has been used to assess IR, but the cut-off points for obese adolescents need to be established. **Purpose:** This study aims to analyze the TyG-index as a marker of IR in obese adolescents. **Methods:** A cross-sectional study was conducted on obese adolescents aged between 13 and 18 years in secondary school. Anthropometric measurements were performed to measure their lipid profile, fasting blood glucose, and insulin level. Homeostatic model assessment for insulin resistance (HOMA-IR) was calculated using the formula: [glucose (mg/dL) x Insulin (μu/L)]/405, with a cut-off value being >3.43 for both sexes, which is suitable for the adolescent population. Meanwhile, the TyG index was calculated using the formula: $TyG = Ln \ [TG \ (mg/dl) \times FBG \ (mg/dl)]/2$. Receiving operation characteristic (ROC) analysis was carried out to determine the area under curve (AUC) and cut-off points of IR for TyG index, which is determined by the largest value of the Youden's index. **Results:** A total of 256 adolescents with obesity participated in this study. Out of 256 participants, 153 (59.8%) were non-IR, while 103 (40.2%) had IR. The male-to-female ratio was 144 to 112. The TyG index was significantly higher in participants with IR than without IR (4.63 ± 0.25 vs 4.46 ± 0.26; p < 0.05). The HOMA-IR correlated positively with the TyG index (r = 0.397; p = 0.000). The AUC of the TyG index was 0.703 (p = 0.000; 95% CI [0.639-0.770]). The best cut-off point for the TyG index to determine IR was >4.50, with a sensitivity of 70.3% and specificity of 63.23%. **Conclusion:** The TyG index was found to be a useful alternative marker for assessing IR in obese adolescents, with the best cut-off point of ≥4.50. .

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Highlights

1. Obesity is a global epidemic problem, with comorbidity such as cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM), and cancers.
2. Obesity leads to insulin resistance, which then causes metabolic syndrome (MetS).
3. Obesity via insulin resistances stimulates fatty acid synthesis, lead to hypertriglyceridemia, and also involves in glucose metabolism and causes glucose intolerant.

BACKGROUND

Insulin plays a significant role in blood glucose regulation by inducing glucose uptake in insulin-sensitive tissues such as muscles, adipocytes, and the heart, consequently reducing blood glue levels. It also inhibits glucose production in organs like the liver, kidneys, and small intestine. Moreover, insulin stimulates the synthesis of fatty acids and glycogen to improve microcirculation (Ye, 2013). However, in certain medical conditions such as obesity, its crucial role is not fully performed due to insulin insensitivity, leading to a condition known as insulin resistance (IR). The accumulation of diacylglycerol (triglycerides) in the liver or skeletal muscles is one of the causes of IR (Samuel and Shulman, 2012). This has become a common occurrence in obese children and adolescents.

Various methods have been used to assess IR. Hyperinsulin-euglycemic clamp (HEC) is considered the gold standard for evaluating insulin sensitivity (DeFronzo et al., 1979). Homeostatic model assessment for insulin resistance (HOMA-IR) has been widely used in clinical practice and epidemiological studies due to its ease, speed, and cost-effectiveness (de Morais et al., 2016). It serves as a validated surrogate measure for IR and type 2 diabetes mellitus in adults with obesity (D'Annunzio et al., 2009). In addition, it has been frequently utilized to screen for IR in high-risk communities as early detection is essential to prevent IR-related comorbidities. However, it is important to note that the cut-off points for HOMA-IR vary according to factors such as race, age, and gender (Tang et al., 2015).

The HOMA-IR requires fasting insulin levels as one of its components, which can be costly for individuals with limited income. Therefore, for practical purposes, alternative assessment methods are still needed to determine IR, especially in the obese adolescent population. This is crucial as it can serve as a preventive marker for future medical interventions and health policies. In recent years, the triglyceride glucose (TyG) index has been used as an alternative method to assess IR. This is because elevated triglyceride (TG) levels can interfere with glucose metabolism and are associated with impaired glucose sensitivity, a condition known as diabetic dyslipidemia (Parhofer, 2015). Research has shown that the TyG index is a cost-effective means of estimating IR.

OBJECTIVE

In this study, the TyG index was used to evaluate IR, while the HOMA-IR was used as a reference. This study also established correlations between the TyG index and HOMA-IR, and it identified appropriate cut-off points to assess IR in the obese adolescent population using a receiver operating characteristic (ROC) curve.

MATERIAL AND METHOD

Study design

A cross-sectional study was conducted in Surabaya and Sidoarjo from October 2019 to January 2020, involving obese adolescents aged between 13 and 18 years as the participants. Individuals who had taken corticosteroids or dyslipidemia drugs within the six months before the study or those experiencing infections or immune/endocrine disorders were excluded from the study. Meanwhile, individuals who did not take antibiotics, smoke, undergo hormonal therapy, or consume alcohol or drugs that could impact body composition were included in the study.

Sample size determination

The required number of participants was calculated using the following formula:

$$n = \left[\frac{\left(Z_{1-\alpha/2} + Z_{1-\beta} \right)}{½ \ln \left[\!\left[\frac{[(1 + r)]\!]}{1 - r} \right]\right.} \right]^2 + 3$$

Based on this calculation, the number of participants required for this study was 260.

HOMA-IR calculation

To distinguish between participants with IR and those without IR, the HOMA-IR was calculated using the following formula:

$$HOMA - IR \ \equiv \left[Fasting\ blood\ glucose\ \left(\frac{mg}{dL}\right) \times insulin\ \left(\frac{\mu u}{L}\right) \right] \div 405$$

The cut-off point to define IR was >5.22 for male adolescents and >3.82 for male adolescents, given that the sample consisted of adolescents in the pubertal period with obesity (Kurtoglu et al., 2010).

TyG index calculation

The TyG index was calculated using the following formula (Guerrero-Romero et al., 2010; Simental-Mendía and Guerrero-Romero, 2020):

$$TyG - index = Ln \left[TG\ \left(\frac{mg}{dL}\right) \times FBG\ \left(\frac{mg}{dl}\right) \right] \div 2$$

TG stands for triglyceride, and FBG stands for fasting blood glucose.

Statistical analysis

Normality tests and Levene's test were conducted to evaluate the distribution and homogeneity of the variables. Variables with normal distribution and homogenous variance were subjected to independent samples t-test and Fischer's exact test according to sex. Meanwhile, variables that did not show a normal distribution nor homogenous variance were analyzed using the Mann-Witney U test. Furthermore, Spearman's rank correlation analysis was carried out to determine the relationships between the TyG index and HOMA-IR as well as with lipid profile, blood pressure, blood glucose, and anthropometric obesity markers. Receiving operation characteristic (ROC) analysis was also carried out to define the area under the curve (AUC) and cut-off points for IR using the TyG index based on the largest value of Youden's index.

Ethical clearance

The study has been reviewed and declare to be ethically appropriate by Health Research Ethics Committee of Universitas Airlangga, School of Medicine number 0411/KEPK/VII/2018.

RESULT

A total of 256 obese adolescents participated in this study, with a prevalence of IR at 40.23%. In the IR group, the youngest participant was 12 years and 3 months old, while the oldest was 18 years and 10 months old, with an average of 15 years and 1 month old. Meanwhile, in the non-IR group, the youngest participant was 12 years and 6 months old, while the oldest was 18 years and 7 months old, with an average of 14 years and 11 months old. A summary of the characteristics of the participants is provided in Table 1.

Table 1. Characteristics of the participants (n = 256)

Characteristic of subject	IR (n = 103)	Non-IR (n = 153)	p-value
Sex			0.029[1]
- Male	49 (47.57%)	95 (62.09%)	
- Female	54 (52.43%)	58 (38.91%)	
Age (months)	178.75 ± 18.16	180.69 ± 16.98	0.383

Body weight (kg)	85.92 ± 12.25	81.97 ± 13.69	0.011
Body height (cm)	160.61 ± 7.40	160.79 ± 7.98	0.759
BMI (kg/m^2)	31.61 ± 3.80	32.19 ± 4.28	0.007
Waist circumference (cm)	99.48 ± 11.28	96.52 ± 9.711	0.048[3]
Hip circumference (cm)	109.91 ± 10.40	106.35 ± 8.58	0.003
Waist-to-hip ratio (WHR)	0.905 ± 0.072	0.908 ± 0.069	0.730
Waist-to-height ratio (WHtR)	0.619 ± 0.066	0.600 ± 0.056	0.012
FBG (mg/dl)	87.17 ± 8.19	83.82 ± 6.36	0.000
Fasting insulin	34.67 ± 15.89	14.35 ± 4.49	0.000[3]
Adiponectin (µg/dl)	11.77 ± 5.65	14.10 ± 7.26	0.048[3]
Total cholesterol (mg/dl)	181.33 ± 32.06	168.02 ± 31.41	0.001
LDL-C (mg/dl)	120.64 ± 28.62	109.44 ± 26.59	0.002
HDL-C (mg/dl)	41.82 ± 8.31	44.38 ± 7.21	0.010
Triglyceride (mg/dl)	136.41 ± 59.31	101.89 ± 59.31	0.000
Systolic blood pressure (mmHg)	126.00 ± 12.15	122.60 ± 13.68	0.043
Diastolic blood pressure (mmHg)	82.32 ± 10.60	81.33 ± 9.98	0.447
HOMA-IR	7.48 ± 3.61	2.96 ± 0.94	0.000[3]
TyG index	4.63 ± 0.25	4.46 ± 0.26	0.000

Paired sample t-test; [1]Fischer's exact test; [3]Mann-Witney U test, significant at $p < 0.05$

The results showed that there was no significant difference in age, body height, waist-to-hip ratio (WHR), and diastolic blood pressure between the two groups. However, the other parameters showed a significant difference between participants with IR and without IR. The HOMA-IR was positively correlated with the TyG index ($r = 0.397$; $p = 0.000$). Table 2 provides a summary of the correlation analysis between the HOMA-IR and TyG index as well as with anthropometric obesity markers, lipid profile, fasting blood glucose (FBG), and blood pressure.

The HOMA-IR was positively correlated with all anthropometric obesity markers, FBG, insulin levels, lipid profiles, and systolic blood pressure ($p < 0.05$). However, it was not correlated with diastolic blood pressure ($p > 0.05$). In contrast to the HOMA-IR, the TyG index was not correlated with any anthropometric obesity markers and blood pressure ($p > 0.05$). However, it was correlated with FBG, fasting insulin, adiponectin, and lipid profiles ($p < 0.05$).

Table 2. Spearman's rank correlation between the HOMA-IR and TyG index as well as with anthropometric obesity markers, lipid profile, blood glucose, and blood pressure in obese adolescents (n = 256)

Variables	HOMA-IR		TyG index	
	r	p	r	p
BMI (kg/m^2)	0.240**	0.000	0.083	0.185
Waist circumference (cm)	0.284**	0.000	0.085	0.173
Hip circumference (cm)	0.286**	0.000	0.076	0.225
WHtR	0.248**	0.000	0.036	0.565
FBG (mg/dl)	0.287**	0.000	0.135*	0.031
Fasting insulin	0.987**	0.000	0.387**	0.000
Adiponectin (µg/dl)	-0.168**	0.007	-0.215**	0.001
Total cholesterol (mg/dl)	0.191**	0.002	0.467**	0.000
LDL-C (mg/dl)	0.185**	0.003	0.366**	0.000
HDL-C (mg/dl)	-0.222**	0.000	-0.278**	0.000
Triglyceride (mg/dl)	0.354**	0.000	0.988**	0.000
Systolic blood pressure (mmHg)	0.182**	0.003	0.121	0.054
Diastolic blood pressure (mmHg)	0.073	0.246	-0.017	0.756

Furthermore, linear regression analysis confirmed that the HOMA-IR was influenced by anthropometric obesity markers although the influence was not significant ($p < 0.05$) at only 3.1-6.1%. In contrast, the TyG-index did not show any correlation with anthropometric obesity markers ($p < 0.05$). In addition, both HOMA-IR and TyG index were negatively correlated with adiponectin, although not significant. Adiponectin influenced the TyG index by 2.6% ($p = 0.010$), which could be mathematically modeled

as [(4.605) + (-0.006)] x (adiponectin). Similarly, adiponectin influenced the HOMA-IR by 2.8% (p = 0.007), which could be mathematically modeled as [(5.7777) + (-0.076)] x (adiponectin).

Table 3. Linear regression analysis of the HOMA-IR and TyG-index as well as with anthropometric obesity markers (n = 256)

Dependent variables	HOMA-IR				TyG index			
	R^2	β	p	CI	R^2	β	p	CI
Body weight	0.037	0.191	0.002	0.017-0.075	0.012	0.111	0.076	0.000-0.005
BMI	0.031	0.176	0.005	0.041-0.227	0.065	0.065	0.302	-0.004-0.012
WC	0.061	0.247	0.000	0.040-0.115	0.001	0.027	0.665	-0.002-0.004
HC	0.042	0.204	0.001	0.029-0.112	0.002	0.045	0.471	-0.002-0.005
WHtR	0.054	0.233	0.000	6.056-18.988	0.000	-0.018	0.774	-0.631-0.470

The area under the curve (AUC) for the TyG index to determine IR was found to be 0.704 (p = 0.000, 95% CI [0.639-0.770]). The largest value of Youden's index (1.3352) indicated a cut-off value of $\geq$4.50, with a sensitivity of 70% and specificity of 63.23%.
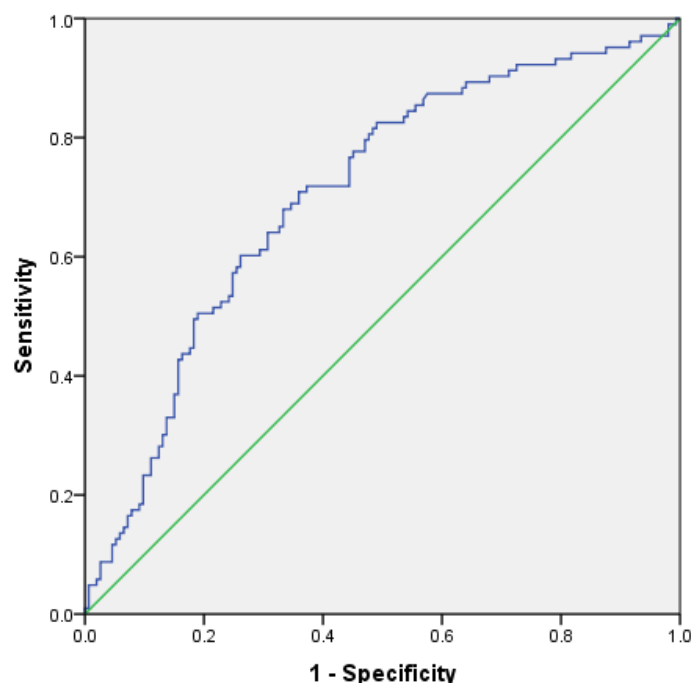

Figure 1. Receiving operation curve (ROC) of TyG index to determine IR in obese adolescents.

DISCUSSION

Lipid changes have been found to impair glucose metabolism, particularly hypertriglyceridemia and low levels of high-density lipoprotein cholesterol (HDL-C), which results in elevated free fatty acids (FFA). This, in turn, can induce insulin resistance by disrupting the cascade that links insulin receptors with glucose transporters. Hypertriglyceridemia is also associated with inflammation, which further contributes to IR. HDL-C directly influences glucose metabolism by inducing reverse cholesterol transport and altering the intracellular lipid environment, thereby reducing the micro-inflammation (Parhofer, 2015). The presence of IR is strongly correlated with fat accumulation in the abdomen, a characteristic of central obesity (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001). The HOMA-IR has also been used as a marker for metabolic syndrome (MetS) in clinical and epidemiological studies (De Abreu et al., 2017).

IR is a significant disorder among young obese adolescents as it increases the risk of developing MetS, type 2 diabetes mellitus, and cardiovascular diseases in adulthood. Insulin plays a crucial role in

reducing blood glucose levels and stimulating the synthesis of fatty acids and glycogen. Insulin also promotes mitochondrial function and enhances microcirculation. In cases of IR, hyperinsulinemia occurs, where an excessive amount of insulin is produced to control blood glucose levels. IR tends to develop before the onset of type 2 diabetes mellitus. This results from various factors including obesity, inflammation, mitochondria dysfunction, hyperinsulinemia, lipodystrophy, and hyperlipidemia (Ye, 2013). However, the incidence of IR is strongly influenced by factors such as puberty, gender, and race/ethnicity. Early onset of IR typically occurs during puberty or Tanner stage 2, with its peak at Tanner stage 3 in all sexes and a subsequent decline at Tanner stage 5. Nevertheless, it is important to note that girls tend to have a higher prevalence of IR than boys (Moran et al., 1999).

The HOMA-IR has been widely used to assess IR, but there is a lack of consensus regarding cut-off points for children and adolescents. The values tend to vary throughout different life stages, particularly during childhood and adolescence when fasting insulin and blood glucose levels fluctuate (Romualdo et al., 2014). Previous studies have suggested that the cut-off points for the HOMA-IR were determined according to pubertal stages. For example, some suggested a cut-off point at ≥ 2.6 for prepubertal children (Burrows et al., 2015; Yin et al., 2013), while others suggested a cut-off point at ≥ 4 for pubertal adolescents without using the ROC curve (Yin et al., 2013). In addition, other studies set cut-off points at >5.22 for boys and >3.82 for girls during puberty, using the oral glucose tolerance test (OGTT) as a reference (Andrade et al., 2016; Kurtoglu et al., 2010). However, it is important to note that OGTT is primarily used to assess glucose tolerance and may not be the ideal method to determine IR (Basila et al., 2011). In a study conducted in Korea, the cut-off points for HOMA-IR were set at 3.6 for girls and 3.8 for boys (Chu et al., 2019), while in China, a higher value of >4.59 was proposed (Liang et al., 2015). These variations in cut-off points for HOMA-IR depend on factors such as age or pubertal status, gender, and race/ ethnicity.

The correlation between the HOMA-IR and TyG index aligns with the results from other studies (Aslan Çin et al., 2020; Kimm et al., 2010; Locateli et al., 2019; Özkaya et al., 2014). In addition, the HOMA-IR was correlated with BMI, waist circumference, waist-to-height ratio (WHtR), and hip circumference, which was also found in other studies (Mirzaalian et al., 2019). The correlation between HOMA-IR and systolic blood pressure, but not with diastolic blood pressure, was also found in another study (Mirzaalian et al., 2019). In terms of lipid profile, this study revealed a correlation between the HOMA-IR and all lipid profiles. This finding is consistent with research conducted in Chinese adults without diabetes, which showed correlations between the HOMA-IR and TG and HDL-C (Zheng et al., 2017). Similarly, another study in India involving subjects aged between 18 and 60 years showed significant correlations between the HOMA-IR and all lipid profiles (Singhal and Bansal, 2018). Furthermore, this study aligns with other studies that demonstrated a negative correlation between the HOMA-IR and adiponectin (Karimi et al., 2019), despite the insignificant correlation coefficient.

The cut-off point for the TyG index to determine IR in this study is much lower than in other studies (Aslan Çin et al., 2020; Kimm et al., 2010; Locateli et al., 2019; Özkaya et al., 2014). However, this particular cut-off point aligns with the initial study of the TyG index conducted in healthy adults (4.50 vs 4.65) (Simental-Mendía et al., 2008). It is important to note that the initial publication of the TyG index formula contained an error. Despite the error, the formula still yielded good results as a surrogate for IR, although the values differed (Simental-Mendía and Guerrero-Romero, 2020). In this study, the TyG index was correlated with lipid profile, which is consistent with the results of other studies, (Simental-Mendía et al., 2008) as well as with adiponectin. However, it was not correlated with blood pressure and anthropometric obesity markers. The AUC of the TyG index falls within the preferred range of 7.0 to 8.0, making it a suitable surrogate to identify IR in obese adolescents. Nevertheless, further research is needed to determine the effectiveness of the TyG index concerning gender and puberty.

Limitations

This study did not investigate chemokine markers such as adiponectin.

CONCLUSION

The TyG index is a useful alternative marker for assessing IR in obese adolescents, with the best cut-off point being $\geq$4.50.

Conflict of interest

The author declares no conflict of interest regarding the content of this study, authorship, and/or publication of this article.

Ethical clearance

This study was approved by the Ethics Committee of the Faculty of Medicine, Universitas Airlangga (No. 0411/KEPK/VII/2018).

Funding

No funding was received for conducting this study.

Author Contribution

RI responsibles for data collection, data analysis, and drafting, supervising of the study and proofreads the manuscript.

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