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Triglyceride-Glucose index as a surrogate marker for insulin resistance in obese adolescents

Obez adolesanlarda insülin direncinin göstergesi olarak olarak Trigliserit-Glikoz indeksi

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SUMMARY

Objective: There is a lot of study in adults investigating the Triglyceride-Glucose (Ty-G) index. However, a limited study has been searched in the pediatric age group. Moreover, to the best of our knowledge, there is no study on Turkish children. The aim of this study, to investigate the usability of the triglyceride-glucose index as an indicator of insulin resistance in obese adolescents and to calculate the cut-off values.

Method: Six hundred twenty-three pubertal obese adolescents (266 boys, and 357 girls) were retrospectively evaluated. Ty-G index and HOMA-IR levels were calculated. ROC analysis was used for the estimations of the Ty-G index cutoff value.

Results: There was positive correlation between HOMA-IR and Ty-G index in boys ($r=0.255$, $p<0.001$), in girls ($r=0.402$, $p<0.001$), and all study groups ($r=0.323$, $p<0.001$). Ty-G index cutoff value for insülin resistance in pubertal obese adolescents was calculated as 8.42 with 70.1 % sensitivity and 59.3 % specificity for all study groups; 8,38 with 71.1 % sensitivity, and 48.3 % specificity for boys; 8,27 with 80% sensitivity, and 52.9% specificity for girls.

Conclusions: Ty-G index may be a reliable indicator for insülin resistance in pubertal obese adolescents. More attention should be given fort his marker with prospective studies.

Keywords: Insulin resistance, Triglyceride-Glucose index, HOMA-IR, obesity, adolescents.

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ÖZET

Amaç: Trigliserit-Glikoz (Ty-G) indeksini araştıran yetişkinlerde çok sayıda çalışma olmasına rağmen çocukluk yaş grubunda sınırlı sayıda çalışma vardır. Ayrıca bildiğimiz kadarıyla Türk çocukları ile ilgili bir çalışma bulunmamaktadır. Bu çalışmanın amacı, obez adolesanlarda Ty-G indeksinin insülin direncinin bir göstergesi olarak kullanılabilirliğini araştırmak kesme değerlerini hesaplamaktır.

Yöntem: Altı yüz yirmi üç obez ergen (266 erkek ve 357 kız) geriye dönük olarak değerlendirildi. Ty-G indeksi ve HOMA-IR seviyeleri hesaplandı. Ty-G indeks kesme değerinin tahminleri için ROC analizi kullanıldı.

Bulgular: Erkeklerde ($r=0.255$, $p<0.001$), kızlarda ($r=0.402$, $p<0.001$) ve tüm çalışma gruplarında ($r=0.323$, $p<0.001$) HOMA-IR ile Ty-G indeksi arasında pozitif korelasyon vardı. Pubertal obez ergenlerde insülin direnci için Ty-G indeksi eşik değeri tüm çalışma grupları için %70.1 duyarlılık ve %59.3 özgüllük ile 8.42 olarak; erkek adolesanlar için %71,1 duyarlılık ve %48,3 özgüllük ile 8,38 olarak; kızlar için %80 duyarlılık ve %52.9 özgüllük ile 8,27 olarak hesaplandı.

Sonuç: Ty-G indeksi pubertal obez ergenlerde insülin direnci için güvenilir bir gösterge olabilir. Bu konuda prospektif çalışmalara ihtiyaç vardır.

Anahtar sözcükler: İnsülin direnci, Trigliserit-Glikoz İndeksi, HOMA-IR, obezite, ergen.

INTRODUCTION

Obesity is a chronic disease that has an increasing prevalence in both developed and developing countries and affects adults and children[1]. Therefore, prevention and treatment of obesity and early recognition of obesity-related diseases have gained importance.

Obesity is an important risk factor for the development of some chronic diseases such as insulin resistance, hypertension, and type 2 diabetes[2-3]. Insulin sensitivity is inversely related to body mass index and body fat. Insulin resistance can be defined as impairment of the normal biological response to both endogenous and exogenous insulin. One of the primary defects underlying the development of type 2 diabetes is thought to be insulin resistance. So, it is present in 85% of these patients with Type 2 DM. It is also related to the pathogenesis of many illnesses which includes coronary heart disease, and hypertension [4].

There are several methods for measuring IR[5-7]. The hyperinsulinemic-euglycemic clamp test is accepted as a gold standard method though it is too complex and time-consuming method[5]. So, some mathematical formulas have been developed for measuring insulin sensitivity. One of the most widely used methods is the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), which is calculated using fasting glucose and fasting insulin[6]. The biggest limitation of the HOMA-IR test is that insulin cannot be studied in every center, especially in primary care centers. Therefore, it was needed a simple, reliable, and less costly method of measuring insulin resistance. Simental-Mendia et al. developed the Ty-G index[7]. The Ty-G index is a calculation method measured using triglyceride and fasting blood glucose. Studies have shown that insulin resistance measured by the hyperinsulinemic-euglycemic clamp method is highly correlated with HOMA-IR[7-8]. It was reported that the Ty-G index showed a higher correlation with the hyperinsulinemic-euglycemic clamp test compared to the HOMA-IR[5-9]. However, there are limited studies on the use of the Ty-G index as an indicator of insulin resistance in the pediatric population.

The study is to investigate the usability of the Ty-G index as an indicator of insulin resistance in obese adolescents and to try to determine the cut-off values.

MATERIAL AND METHODS

The study was conducted at Sivas Cumhuriyet University Medical Faculty. The population of the study consisted of 623 pubertal obese children (266 boys, 357 girls) aged 10-18 years old. Patients were selected retrospectively from the pediatric endocrinology department archive between January 2015 to January 2021. Body mass index (BMI) was calculated according to the formula [weight (kg)/height $(m)^2$]. Weight, height, and BMI are expressed as the z-score. Obesity was defined as a BMI above the 95th percentile for the sex and age, according to percentile charts for Turkish children[10]. Children who have the chronic disorder or secondary obesity, prepubertal status, used any medication were excluded.

Laboratory analysis

Overnight fasting blood samples were obtained between 8:00 and 8:30 a.m. in serum-separating gel tubes (Becton Dickinson, UK). Glucose, total cholesterol, triglyceride, low-density lipoprotein cholesterol (LDL), and high-density lipoprotein cholesterol (HDL) levels were measured using a colorimetric method (Roche Cobas, c702,

Germany). Insulin levels were measured using the electrochemiluminescence method (Roche Cobas e801, Germany).

Calculations

1. Triglyceride Glucose index (Ty-G İndex): it was calculated as the following formula[7]

"Ln[fasting triglycerides (mg/dl)×fasting plasma glucose (mg/dl)/2])"

2. Homeostasis Model of Insulin Resistance (HOMA-IR): According to the HOMA-IR level, the threshold value for insulin resistance was taken as 3.82 in girls and 5.22 in boys[11]. It was calculated using the following formula[6].

"HOMA-IR=[FastinG insulin level (μU/mL)xFasting glucose level (mg/dL)]/405]"

Statistical analyses

Statistical analyses of the data were carried out with Statistical Package for Social Sciences (SPSS/PC 16.0) for Windows software (SPSS, Chicago, IL, USA). The results were analyzed using the percentage distribution for qualitative data and mean (standard deviation) for quantitative data. The statistical tests included the Shapiro-Wilks test for normality, the chi-square test for comparisons of qualitative data among groups, and the independent samples *t*-test of quantitative data among gender groups. The correlations between quantitative data were calculated by Pearson rank correlations. ROC analysis was used for the estimations of the Ty-G İndex cutoff value. The significance level was accepted as $p<0.05$.

The institutional ethics committee approved the study protocol (20.10.2021/2021-10/02).

RESULTS

The mean age of the study population was 13.31±1.98 years (13.11±1.92 for boys, 13,45±2,02 for girls, p=0.03). Forty-two percent of the study population (n=357) was girl. Weight, weight-SDS, Height, height-SDS, BMI, and BMI-SDS levels were shown in Table 1. When we compared according to genders, serum glucose (89,48±7,31 vs. 87,56±7,66 mg/dL), and cholesterol (158,66±32,81 vs. 152,77±28,79) levels were higher in boys than girls (p=0.002 and p=0.01, respectively). However, serum insülin, HDL, LDL, and triglyceride levels were similar (p>0.05). (Table1.)

Table 1. Basal metabolic and metabolic parameters of the study group

	All	Boys	Girls	p
Age, *year*	13.31±1.98	13.11±1.92	13,45±2,02	0,03
Sex		%58	%42	<0,01
Body-weight, *kg*	72,59±18,32	74,94±20.59	70,83±16,24	<0.001
Body-weight-SDS	2,58±0,92	2,42±0,83	2,70±0,96	<0.001
Height, *cm*	155,42±12,58	156,79±13,61	154,39±11,67	0,01
Height-SDS	0,49±1,15	0,73±1,07	0,31±1,17	<0,001
BMI, kg/cm^2	29,68±4,09	29,90±4,07	29,51±4,11	0,24
BMI-SDS	2,47±0,53	2,37±0,48	2,55±0,55	<0,001
Glucose, *mg/dL*	88,37±7,57	89,48±7,31	87,56±7,66	0,002
Insulin,*Uu/mL*	23,36±13,95	23,14±16,57	23,53±11,64	0,73
Cholesterol, *mg/dL*	155,29±30,69	158,66±32,81	152,77±28,79	0,01
HDL, *mg/dL*	43,97±10,66	43,01±9,62	44,68±11,33	0,05
LDL, *mg/dL*	97,28±27,51	99,36±27,57	95,69±27,39	0,11
Triglyceride, *mg/dL*	120,12±53,05	121,98±58,01	118,73±49,03	0,45
HOMA-IR	5,16±3,28	5,19±3,88	5,14±2,75	0,84
TG-Index	8,47±0,46	8,48±0,501	8,46±0,44	0,66

HOMA-IR levels of the all study group was 5,16±3,28. When we compared HOMA-IR levels in boys and girls, there is no statistically significant difference (5,19±3,88 vs 5,14±2,75; p>0.05). Similarly, Ty-G index levels were also similar in the groups (8,47±0,46 for all study groups, 8,48±0,501 for boys, and 8,46±0,44 for girls; p>0.05). (Table 1, Figure 1).

When we evaluated the correlations between HOMA-IR and Ty-G index; there were statistically

significant positive correlations in boys (r=0.255, p<0.001), girls (r=0.402, p<0.001), and all study groups (r=0.323, p<0.001), (Figure 2). It has been also shown that HOMA-IR level was positively correlated with age, BMI-SDS, Glucose, insülin, and triglyceride; negatively correlated with HDL levels. On the other hand, there was a weak correlation between Ty-G İndex with insülin, cholesterol LDL, and HDL levels (Table 2).

Ty-G index cutoff value for insülin resistance in pubertal obese children was calculated as 8.42 with 70.1 % sensitivity and 59.3 % specificity for all study groups; 8,38 with 71.1 % sensitivity, and 48.3 % specificity for boys; 8,27 with 80% sensitivity, and 52.9% specificity for girls (Figure 3).

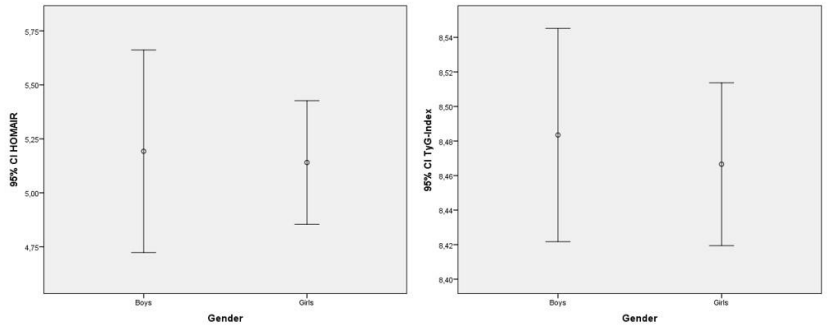

Figure 1: Comparison of the HOMA-IR and Ty-G index according to gender

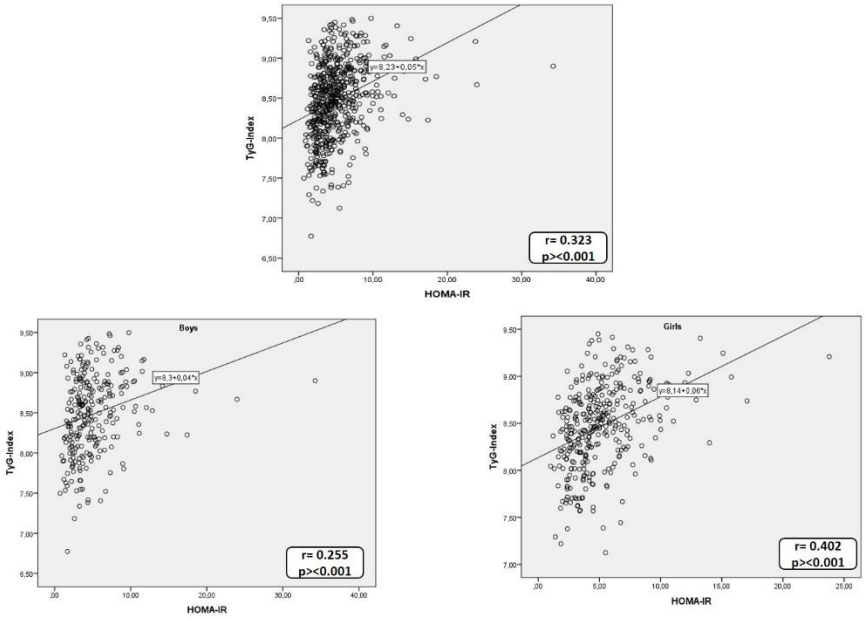

Figure 2: Correlations between HOMA-IR and Ty-G ındex; there were statistically significant positive correlations in boys (r=0.255, p<0.001), girls (r=0.402, p<0.001), and all study groups (r=0.323, p<0.001)

Table 2: Pearson correlation coefficients between HOMA-IR and Ty-G index with metabolic parameters

	All Individuals				Boys				Girls			
	HOMAIR		TG-INDEX		HOMAIR		TG-INDEX		HOMAIR		TG-INDEX	
	r	p	r	p	r	p	r	p	r	p	r	p
Age, *year*	0,139	0,001	-0,030	ns	0,256	<0,001	0,043	ns	0,028	ns	-0,086	ns
BMI-SDS	0,288	<0,001	0,053	ns	0,225	<0,001	-0,009	ns	0,373	<0,001	0,106	ns
Glucose, *mg/dL*	0,346	<0,001	0,205	<0,001	0,305	<0,001	0,101	ns	0,404	<0,001	0,289	<0,001
Insulin,*Uu/mL*	0,984	<0,001	0,317	<0,001	0,989	<0,001	0,260	<0,001	0,979	<0,001	0,387	<0,001
Cholesterol*, mg/dL*	0,034	ns	0,314	<0,001	-0,029	ns	0,326	<0,001	0,108	0,04	0,303	<0,001
HDL, *mg/dL*	-0,155	<0,001	-0,368	<0,001	-0,154	0,013	-0,408	<0,001	-0,165	0,002	-0,346	<0,001
LDL, *mg/dL*	0,048	ns	0,246	<0,001	-0,029	ns	0,274	<0,001	0,127	0,021	0,224	<0,001
Triglyceride, *mg/dL*	0,253	<0,001	0,945	<0,001	0,183	0,003	0,946	<0,001	0,346	<0,001	0,944	<0,001

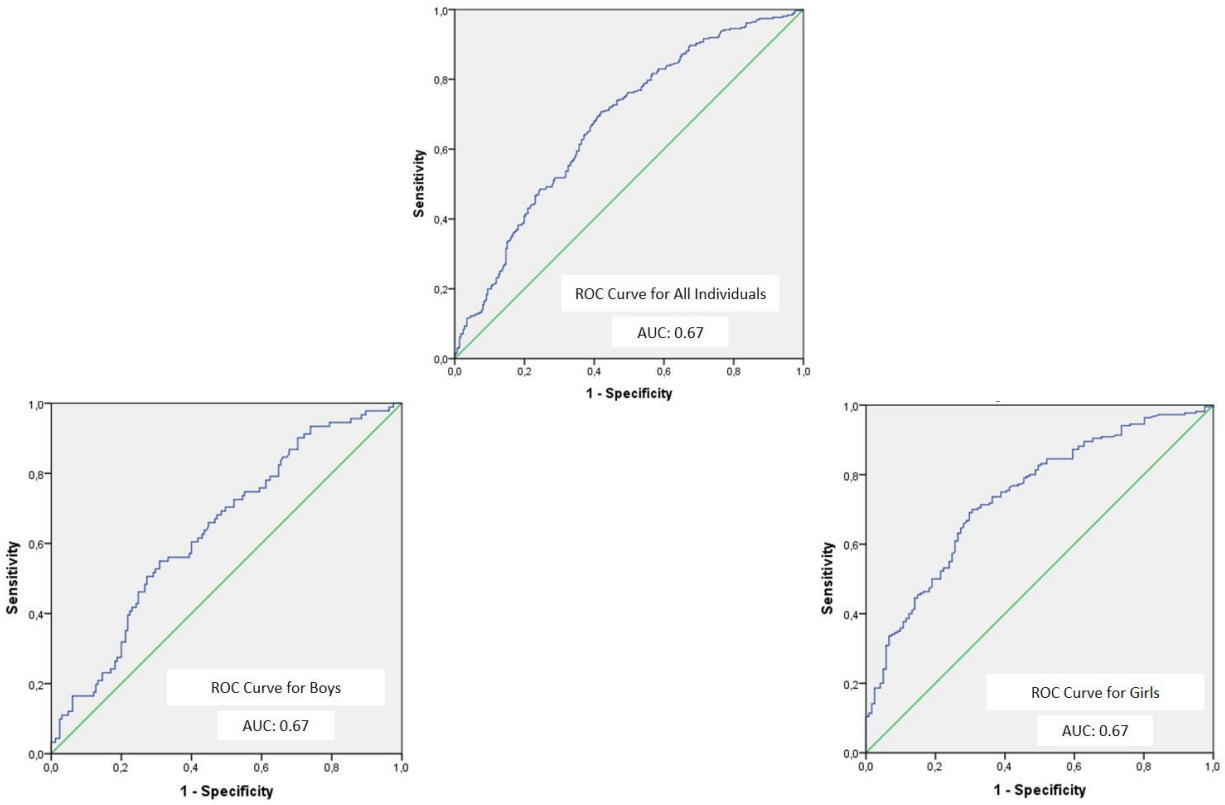

Figure 3: Receiver operating characteristic (ROC) curve of the effect of Ty-G index on detection of insulin resistance; It was calculated as 8.42 with 70.1 % sensitivity and 59.3 % specificity for all study groups; 8,38 with 71.1 % sensitivity, and 48.3 % specificity for boys; 8,27 with 80% sensitivity, and 52.9% specificity for girls

DISCUSSION

In this study, we found Ty-G index cutoff value for insülin resistance in pubertal obese children was 8.42 for all study groups, 8,38 for boys, and 8,27 for girls. On the other hand, there were significant correlations between Ty-G index and metabolic syndrome criteria (fasting insülin, cholesterol LDL, and HDL levels)

Insulin resistance is one of the most important factors in the pathogenesis of obesity-related metabolic complications, especially in Type 2 DM. In insulin resistance, there is a decrease in glucose uptake by muscle and adipose tissue, and suppression of hepatic glucose secretion[12]. The euglycemic clamp test is the recommended gold standard test for the diagnosis of insulin resistance in children and adolescents[14]. However, it is only used for research. Another frequently used method for assessing IR, in the oral glucose tolerance test, blood must be drawn at least 5 times, so it is time-intensive and not an easily practicable method because it is an invasive procedure. Because of these limitations, researchers have searched for easy-to-apply, simple, and highly specific tests for the investigation of IR, such as HOMA-IR, quantitative insulin sensitivity check index (QUICKI), and fasting glucose-insulin ratio (FGIR)[14]. There is no consensus on which cut-off should be taken in children and adolescents for HOMA-IR, which is one of the most used methods. On the other hand, it has an important limitation, because of the cut-off point changed by the pubertal stage. Recently, emerged studies have shown that the Ty-G index can accept as a marker of IR, that is correlated with both the euglycemic clamp test and the HOMA-IR levels[7-9]

There is a lot of study in adults investigating the Ty-G index[15-18]. However, a limited study in pediatric age group[19-24]. Moreover, to the best of our knowledge, there is no study on Turkish children. Calcaterra et al.[25] found that the cut-off value for the Ty-G index related to IR was considered 7.98 (sensitivity 60%, and specificity 78%; AUC 0.69), in their study of 541 children and adolescents aged

11.7±2.71 yrs. In the same study, the authors suggested that the Ty-G index is not affected by gender and pubertal stage. In our study, we found similar cut-off values for boys and girls (8.38 vs 8.27). Moreover, similar cut-off values have been reached in a limited number of studies conducted in different countries (7.8-8.65)[15-24]. Moon et al.[20] showed that 12-19 years old 8037 adolescents the cut-off values for the Ty-G index ranged from 8.15-8.65 in Mexican American, Non-Hispanic White, Korean, and Non-Hispanic Black adolescents. They also showed that a modest correlation between HOMA-IR and Ty-G index. In a cross-sectional retrospective study, it has been shown that higher central body adiposity and shorter time spent activities were related to increased Ty-G index in prepubertal children, and the calculated cutoff point in this study is found 7.88 (80% sensitivity, 52% specificity)[26].

In a prospective study (followed up for 8.84±4.39 years), Navarro-González et al.[27] showed that Ty-G index is better than triglyceride or fasting glucose level for prediction of the Type 2 diabetes in normoglycemic individuals at baseline. It has been also shown that Ty-G index may be considered as a predictive marker for atherosclerosis, hepatosteatosis, and cardiovascular diseases[28].

There is a strong relationship between adiposity and IR[29]. The prevalence of hepatic steatosis is highly prevalent in Type 2 diabetes patients[30-31]. Ryysy et al.[32] showed that the insülin requirement of patients with Type 2 diabetes is significantly correlated with hepatic fat level. However, the exact mechanism of the insülin resistance in obese individuals has not yet been fully understood. The increased intracellular lipids in Skeletal Muscles may be related to insülin resistance[33].

The study has some limitations. Firstly, we can not evaluate the cases diet because of the retrospective design, Secondly, we diagnosed insülin resistance according to HOMA-IR levels instead of euglycemic clamp test or OGTT.

In conclusion, Ty-G index may be a reliable indicator for insülin resistance in pubertal obese adolescents. More attention should be given fort his marker with prospective studies.

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