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A novel diagnostic tool in determining insulin resistance in obese children: Triglyceride / HDL ratio

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Abstract

Background/Aim: It is known that the frequency of obesity and insulin resistance is increased in children. Diagnostic laboratory criteria of insulin resistance are unclear in children despite the widespread use of the Homeostasis model assessment for insulin resistance (HOMA-IR). Serum triglyceride (TG)/high-density lipoprotein (HDL) ratio is reported to reflect insulin resistance in recent studies. We aimed to investigate the usefulness of the TG/HDL ratio in determining insulin resistance and its correlation with the HOMA-IR index in overweight/obese children.

Methods: Patients who presented to the Pediatric Endocrinology outpatient clinic with excessive weight were examined in this retrospective cohort study. The patients were divided into subgroups according to BMI, sex, pubertal stage, and presence of hepatosteatosis, and the HOMA-IR index and TG/HDL ratios were compared.

Results: One hundred and fifty-nine patients aged 5-18 years, with a mean age of 11.4 (3.13) years, were included in the study. Of the patients, 93 (58%) were girls, 99 (62%) were pubertal, and 141 (88.6%) were obese. Seventy-nine (49.6%) patients had insulin resistance. The mean HOMA-IR and TG/HDL were 3.89 (2.29) and 2.71 (1.86), respectively. A positive correlation was found between HOMA-IR value and TG / HDL ratio (r= 0.283, P<0.001). TG/HDL ratio was significantly higher in patients who had insulin resistance and hepatosteatosis than those who did not (P=0.008, P=0.032 respectively). There was no significant difference regarding TG/HDL ratio between female-male, prepubertal-pubertal, overweight/obese patients. There was no correlation between age, body mass index standard deviation score (SDS), and TG/HDL ratio.

Conclusion: TG/HDL ratio is an easy to use, non-invasive, and useful marker of insulin resistance in overweight/obese children regardless of age, gender, pubertal condition, and body mass index standard deviation score.

Keywords: TG / HDL ratio, Insulin resistance, Obese children

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Ethics Committee Approval
The permission was obtained from Gazi Yaşargil Research and Training Hospital ethics committee with 15.1.2021/614 number.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Introduction

The incidence of obesity in children is gradually increasing due to the widespread high-calorie diet and sedentary lifestyle. Obesity, dyslipidemia, hypertension, and glucose metabolism disorder are all components of metabolic syndrome. Insulin resistance and the presence of metabolic syndrome in children are predictors of type 2 diabetes and cardiovascular diseases [1].

The prevalence of dyslipidemia in obese children in Turkey is 21.5% [2]. Many studies showed that high triglyceride (TG) and low high-density lipoprotein (HDL) levels lead to insulin resistance. High TG in serum activates lipoprotein lipase via heparin. Intravascular lipolysis increases and the tissues are exposed to high free fatty acid. High free fatty acids cause insulin resistance through oxidative stress pathways [3]. Insulin resistance and β-cell dysfunction of the pancreas are the two main causes of type 2 diabetes. It has been reported that low HDL and high TG in the circulation can cause cholesterol accumulation in β cells of the pancreas, cellular toxicity, and impairment in insulin secretion, which can directly cause type 2 diabetes [4].

The gold standard diagnostic method in detecting insulin resistance is the hyperinsulinemic-euglycemic clamp method, but this method has little applicability. Instead, "Homeostasis model assessment for insulin resistance (HOMA-IR)" is widely used in determining insulin resistance in children and adults. The HOMA-IR index is affected by many parameters such as age, gender, puberty, and body mass index (BMI) [5]. The fact that HOMA-IR has different threshold values according to gender and puberty confuses clinical practice from time to time. It has recently been reported that the TG / HDL ratio is an easy, non-invasive and useful marker for determining insulin resistance and cardiovascular disease risk [6]. This study aimed to determine the usability of the TG / HDL ratio in determining insulin resistance and its threshold value in overweight/obese children.

Materials and methods

For this study, permission was obtained from the Gazi Yaşargil Research and Training Hospital ethics committee (decision number: 15.1.2021/614). Overweight/obese patients aged 5-18 years who visited the pediatric endocrinology outpatient clinic in Balıkesir Atatürk City Hospital with the complaint of being overweight were included. Patients with syndromic obesity, Cushing's syndrome, chronic disease, or regular medication use, and abnormal thyroid function tests were excluded. Age, gender, anthropometric measurements, pubertal development, the presence of acanthosis nigricans, laboratory tests (glucose, insulin, TG, HDL, total cholesterol, LDL, AST, ALT), and liver ultrasonography findings were recorded retrospectively from the patient files. Height and weight measurements were made with a digital Harpenden stadiometer. Weight, height, BMI (body weight / height^{2,}) and standard deviation scores (SDS) were calculated. Patients with BMI> 2 SDS were considered obese, those with + 1 / + 2 SDS were considered overweight. Testicular volume in males was measured with a Prader orchidometer. Males with a testicular volume of greater than 4 ml, and females with tanner stage≥2 breast development were considered pubertal. HOMA-IR value was calculated with the formula: Fasting insulin level (μU / mL) x fasting glucose (mg / dL) / 405. If the HOMA-IR value was >2.67 in prepubertal males, >2.22 in females, >5.22 in pubertal males, and >3.82 in females, insulin resistance was considered present [7]. The ratio of TG (mg / dL) to HDL (mg / dL) was recorded as TG/HDL value.

Statistical analysis

The sample size was calculated using G*Power version 3 based on the ability to detect a mean difference of TG/HDL ratio between two groups (with insulin resistance, without insulin resistance). The standard deviation used in the calculation was reported in previous trials (Liang et al.) [5]. A confidence level of 95% (P<0.05) and a power of 80% were used. The calculation yielded a minimum sample size of 139. A further increase of 15% was added to allow for attrition, giving an overall sample size of 159 participants. SPSS 24.0 package program was used for statistical analysis. The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to determine whether the data were normally distributed. Descriptive statistics were used. Mann Whitney U and Kruskal Wallis tests were utilized for the non-normally distributed groups. Spearman correlation analysis was performed to determine the relationship between TG/HDL ratio, age, sex, puberty, HOMA-IR, and other parameters. A P-value of <0.05 was considered statistically significant.

Results

A total of 159 patients aged 5-18 years with a mean age of 11.4 (3.13) years were included in the study. Ninety-three (58%) patients were females, 99 (62%) were pubertal, 18 (11.3%) were overweight, and 141 (88.6%) were obese. The clinical and laboratory characteristics of the patients were shown in Table 1. HOMA-IR was above the threshold value in 79 (49.6%) patients according to gender and pubertal status and insulin resistance were present. Acanthosis nigricans was present in 61 of 79 patients with insulin resistance. In 70 (44%) patients, no fatty liver was detected in ultrasonography. First, second- and third-degree fatty liver were detected in 52 patients, 25 patients, and 2 patients, respectively.

Table 1: The clinical and laboratory finding of patients

	Mean(SD)	(Minimum-Maximum)
Age (year)	11.4(3.13)	(5-18)
Weight (SDS)	2.84(1.05)	(0.13-6.52)
Height (SDS)	0.74(1.27)	(-2.28-6.3)
BMI SDS	2.62(0.63)	(1.1-4.8)
Glucose (mg/dL)	89.71(7.1)	(69-123)
Insulin (μU/mL)	17.71(6.33)	(2-48)
HOMA-IR	3.89(2.29)	(0.44-11.54)
TG/HDL	2.71(1.86)	(0.35-11.28)
Triglyceride (mg/dL)	117.58(61.18)	(28-361)
HDL (mg/dL)	47.68(9.68)	(25-81)
Total Cholesterol (mg/dL)	157.97(32.23)	(42-266)
LDL (mg/dL)	89.15(26.65)	(33-171)
AST (U/L)	23.07(7.31)	(10-62)
ALT (U/L)	22(11.8)	(8-68)

SDS: Standard Deviation Score, BMI: Body Mass Index, HOMA-IR: Homeostasis model assessment for insulin resistance, HDL: High-Density Lipoprotein, TG/HDL: Triglyceride/High-Density Lipoprotein

The mean HOMA-IR value of all patients was 3.89 (2.29), and the mean TG / HDL ratio was 2.71 (1.86) (Table 1). There was no difference in HOMA-IR values between the female-male, overweight/obese patients, and patients with and without fatty liver groups. HOMA-IR values of pubertal patients were significantly higher than those of prepubertal patients

(P<0.001) (Table 2). HOMA-IR was positively correlated with age, weight SDS, BMI SDS, glucose, insulin, TG, and negatively correlated with HDL (Table 3). A positive correlation was found between the HOMA-IR value and the TG/HDL ratio (r=0.283, P<0.001) (Table 3).

Table 2: The comparison of HOMA-IR ve TG/HDL ratio according to groups

	HOMA-IR Median(IQR)	TG/HDL Median(IQR)
male	3.23 (IQR 2.99)	1.92(IQR 1.71)
female	3.24 (IQR 2.81)	2.18(IQR 2.21)
P-value *	0.296	0.268
Prepubertal	2.49(IQR 1.49)	1.89(IQR 1.49)
Pubertal	4.3(IQR 2.85)	2.27(IQR 2.6)
P-value *	<0.001	0.114
No insulin resistance	2.29(IQR 1.29)	1.78(IQR 1.48)
Insulin resistance	5.21(IQR 3.43)	2.63(IQR 2.22)
P-value *	<0.001	0.008
Overweight	2.39(IQR 2.92)	2.07±2.93
Obese	3.32(IQR 2.95)	2.02(IQR2.06)
P-value **	0.118	0.733
No hepatosteatosis	2.92(IQR 2.65)	1.86(IQR 1.48)
Hepatosteatosis	4.15(IQR 3.04)	2.3(IQR 2.61)
P-value *	0.068	0.032

*Mann Whitney U test **Kruskal Wallis test IQR: Interquartile Range, Homa-IR: Homeostasis model assessment for insulin resistance, HDL: High-Density Lipoprotein, TG/HDL: Triglyceride/High-Density Lipoprotein

Table 3: The correlation between HOMA-IR, TG/HDL ratio, and other parameters

	HOMA-IR		TG/HDL	
	r	*P*-value	r	*P*-value
Age (year)	0.306	<0.001	0.14	0.08
Weight SDS	0.296	<0.001	0.079	0.323
Height SDS	0.066	0.415	-0.004	0.957
BMI SDS	0.276	<0.001	0.067	0.403
Glucose (mg/dL)	0.394	<0.001	0.08	0.318
Insulin (µU/mL)	0.986	<0.001	0.281	<0.001
Triglyceride (mg/dL)	0.248	0.002	0.955	<0.001
HDL (mg/dL)	-0.309	<0.001	-0.671	<0.001
Total Cholesterol (mg/dL)	-0.041	0.607	0.199	0.012
LDL (mg/dL)	-0.069	0.388	0.03	0.710
AST (U/L)	-0.211	0.008	0.012	0.886
ALT (U/L)	0.03	0.706	0.09	0.261
TG/HDL	0.283	<0.001		

SDS: Standard Deviation Score, BMI: Body Mass Index, Homa-IR: Homeostasis model assessment for insulin resistance, HDL: High-Density Lipoprotein, TG/HDL: Triglyceride/High-Density Lipoprotein

The TG / HDL ratio was significantly higher in patients with insulin resistance and fatty liver compared to those without (P=0.032) (Table 2). There was no difference in TG/HDL ratio between female-male gender, prepubertal-pubertal, overweight/obese patients (P=0.268 P=0.114 and P=0.733 respectively) (Table 2). There was no correlation between age and TG / HDL ratio, and TG / HDL ratio was positively correlated with insulin, TG, and total cholesterol, and negatively correlated with HDL cholesterol (Table 3).

Discussion

In 2003, McLaughlin reported for the first time that the TG/HDL ratio in white obese patients reflects insulin resistance, but changes with ethnicity [8]. In recent studies, it has been reported that TG/HDL ratio is strongly associated with insulin resistance in white obese children, especially in Korea and Southeast Asia, but not in Hispanic and black children. [9-11]. In this study, the TG/HDL ratio was significantly higher in overweight/obese children with IR compared to those without IR and correlated with HOMA-IR while it did not change according to age, gender, and pubertal status.

In determining insulin resistance, Behiry et al. [12], Iwani et al. [11], and Yoo et al. [1] reported threshold TG/HDL ratios of 1.36, 1.11, and 2, respectively, among 90, 425, and 769 overweight/obese children, respectively. Pacifico et al. [13] stated a TG/HDL ratio cut-off value of 1.98 to indicate insulin resistance and metabolic syndrome among 541 children, 391 of which were obese. According to Di bonito et al. [14], this value was 2.2 among 5505 children, 4417 of which were obese. We could not determine a TG/HDL cut-off due to the low under the ROC curve area. However, TG / HDL ratio was significantly higher in overweight/obese children with IR compared to those without IR.

It is known that the HOMA-IR value, which is widely used to determine insulin resistance in children, varies according to gender, puberty, and BMI SDS. During puberty, physiological temporary insulin resistance occurs. A decrease in insulin sensitivity in the pubertal period causes an increase in insulin secretion.

It has been shown that insulin resistance increases at the beginning of puberty, peaks at Tanner stage 3, and regresses to prepubertal levels at the end of puberty. The reason for this change in insulin secretion at puberty is not fully known, but it is thought to be related to a mechanism that enhances the anabolic effect of insulin and growth hormone during rapid somatic growth [7]. It has been reported that increased pubertal hormones and changes in fat distribution in girls during adolescence cause higher insulin secretion and resistance compared to boys [15]. We found that HOMA-IR is higher in girls and pubertal children, it increases with increasing age and BMI SDS. The HOMA-IR index is calculated based on serum insulin and glucose levels. Therefore, physiological changes in serum insulin levels cause changes in the HOMA-IR index. The serum TG level used in the TG/HDL ratio, which reflects insulin resistance regardless of the serum insulin level, shows a small change according to age and does not change according to puberty and gender (normal value for TG is 75-99 mg / dL between 0-9 years of age, and 90-129 mg/dL thereafter). HDL remains the same in all age groups (35-45 mg / dL) [16]. For this reason, a single threshold value for TG/HDL ratio can be given independently of gender and puberty in children. Iwani et al. [11] reported that TG / HDL ratio was positively correlated with HOMA-IR and TG / HDL does not change with age, gender, and pubertal status in 271 overweight / obese children. Yoo et al. [1] reported that there was a positive correlation between HOMA-IR and TG / HDL. Çin et al. [17] found a positive correlation between TG / HDL ratio and HOMA-IR in obese adolescents. These results are consistent with our study.

We found no differences between overweight and obese patients in terms of TG/HDL ratio. It was higher in those with fatty liver than those without. Sixty-five percent (n: 52) of the patients with liver steatosis had first-degree steatosis, which suggests that the TG/HDL ratio may be an early marker for detecting insulin resistance and fatty liver.

Metabolic syndrome and impaired glucose tolerance are closely related to insulin resistance. In a study with 122 obese children, Krawcyzk et al. [18] reported that the TG / HDL ratio was 2.09 times higher in children with metabolic syndrome than in those without. In a study conducted in our country, the threshold of TG / HDL ratio to indicate metabolic syndrome was 2.16 in 1171 obese adolescents [17]. Manco et al. [19] reported that a TG/HDL ratio above 2.2 is associated with impaired glucose tolerance. In our study, the patients were evaluated in terms of insulin resistance, but not in terms of metabolic syndrome and glucose intolerance. This was thought to cause a limitation in evaluating the results of our study.

Conclusion

TG/HDL ratio is an easy, non-invasive, and useful indicator of insulin resistance independent of age, gender, pubertal status, and BMI SDS in overweight/obese children. Large-scale studies are needed to determine the optimum TG/HDL ratio threshold value in detecting insulin resistance in our country.

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