Pediatr Pol 2024; 99 (3): 203-210
DOI: https://doi.org/10.5114/polp.2024.143267
Submitted: 04.04.2024, Accepted: 16.07.2024, Published: 30.09.2024

PEDIATRIA Polska
Polish Journal of PAEDIATRICS

ORIGINAL PAPER

Evaluation of metabolic score for insulin resistance index as a sensitive marker of insulin resistance and its ability to predict hepatic steatosis in obese children and adolescents. A pilot study

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ABSTRACT

Introduction: The metabolic score for insulin resistance (METS-IR) index could be a sensitive marker of insulin resistance and might predict hepatic steatosis in obese children. The aim of the study was to evaluate the METS-IR index as a sensitive marker of insulin resistance and its ability to predict hepatic steatosis in obese children and adolescents.

Material and methods: A cross-sectional study was conducted with 190 subjects: 50 normal weight, 50 with overweight, and 90 children with obesity. All subjects underwent measurements of height, body weight, body mass index (BMI), waist and hip circumference, and blood pressure. A blood sample was taken for assessment of lipid profile, fasting blood glucose and insulin, and liver enzymes. The homeostatic model assessment for insulin resistance (HOMA-IR), triglyceride-glucose (TyG) index, and METS-IR index were calculated. Abdominal ultrasonography was done to search for fatty liver, to measure subcutaneous fat thickness and visceral fat thickness (VFT). Children were classified into a hepatic steatosis group and a group without hepatic steatosis.

Results: Body mass index, waist hip ratio, body fat percentage, subcutaneous fat thickness, visceral fat, alanine aminotransferase, METS-IR, and TyG index were significantly higher in the hepatic steatosis group than in the group without hepatic steatosis. The metabolic score for insulin resistance was the best independent predictor for hepatic steatosis.

Conclusions: The metabolic score for insulin resistance is a sensitive marker of IR among obese children and adolescents and was found to be a strong predictor for hepatic steatosis. The metabolic score for insulin resistance index has significant and positive correlations with HOMA-IR, TyG index, VFT, fasting insulin, and BMI. It could be a used as a screening tool for hepatic steatosis.

KEY WORDS:

obesity, metabolic score for insulin resistance (METS-IR) index, HOMA-IR, triglyceride-glucose (TyG) index, hepatic steatosis.

INTRODUCTION

Insulin resistance (IR) is a common health issue in medical practice. We can define IR as decreased tissue sensitivity to insulin. Obesity is the primary risk factor for IR. It is well known that IR is predisposed to developing several metabolic disorders, such as hyperglycaemia, hepatic steatosis, dyslipidaemia, and hypertension in obese individuals. Insulin resistance is a state of dysfunction as there is decreased sensitivity and responsiveness to insu-

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lin despite a normal or elevated serum insulin concentration [1]. Not all obese children present IR, while recent evidence supports that insulin resistance could be met even in individuals with normal weight [2, 3]. The causal directions of these relationships remain mostly untested. Fat distribution is a more important factor for IR than total weight. Hence, children with normal weight who have fat around their middle and excess visceral fat can develop IR and hepatic steatosis. For obese children, hyperinsulinaemia is a compensatory mechanism to allow insulin action in mild to moderate IR. Such a defect in insulin signalling not only impairs the utilisation of glucose and lipids, but also causes organ complications like metabolic associated fatty liver disease [1].

The homeostatic model assessment (HOMA) is the most commonly used parameter to evaluate IR. It has the disadvantage that an abnormal HOMA-IR result may be false, especially in the absence of other metabolic disturbance components [4, 5]. To overcome this limitation, the triglyceride-glucose (TyG) index has been developed [6]. The triglyceride-glucose index is considered a reliable alternative biomarker of IR [6]. The triglyceride-glucose index is a very simple screening method to evaluate insulin resistance. It requires an evaluation of fasting triglycerides and fasting plasma glucose (FPG). It is used to predict cardiovascular risks in individuals [7, 8]. Recently, the use of the TyG index, as a predictor of cardiometabolic risk factors in childhood and adolescence, has also increased [9, 10]. Several studies considered the TyG index as a marker of IR to identify adults at risk for non-alcoholic fatty liver disease (NAFLD) [11]. Central IR is located in the liver. Hepatic insulin resistance refers to the impaired suppression of glucose production by insulin in hepatocytes. This usually manifests as impaired fasting glucose and NAFLD [4, 12, 13].

Increasing evidence suggests that the metabolic score for insulin resistance (METS-IR) is a novel indicator to replace the traditional indexes to estimate the IR level. The metabolic score for insulin resistance involved more lipid types, so it evaluated more metabolic status and could represent metabolic status and IR status [14–16]. Hepatic steatosis is characterised by fat accumulation in more than 5% of hepatocytes [17], without excessive alcohol consumption.

The aim of this study was to investigate the association between the HOMA-IR, TyG, and METS-IR indexes as markers of insulin resistance and the ability of METS-IR to predict hepatic steatosis in obese children and adolescents.

MATERIAL AND METHODS

STUDY POPULATION

We performed a cross-sectional study. The study protocol was approved by the Human Ethics Committee of the National Research Centre, and written informed consent was obtained from all children and their parents. We enrolled 190 subjects: 50 normal-weight children 50 children with overweight and 90 with obesity. This study is part of project no. 10010324 carried out in the National Research Centre, Cairo, Egypt. They were recruited from the Paediatrics Clinic at the NRC. All non-obese volunteers were age-matched healthy subjects in apparent good health and taking no medications. A child was obese if their body mass index (BMI) was > 95% percentile for age and gender percentile curves of growth for our population [18]. The studied participants were classified into 3 groups according to body mass index: normal weight (BMI 18.5–24.9), overweight (BMI 25–29.9), and obesity (BMI ≥ 30 kg = m^2).

Exclusion criteria: patients with any of the following criteria were excluded from the study: hepatobiliary diseases, chronic liver diseases including viral hepatitis malignancies, ascites, medications known to cause hepatic steatosis (such as oestrogens, corticosteroids, amiodarone, and valproate; at present or within the last 2 years), anti-inflammatory drugs, inflammatory bowel disease, human immunodeficiency virus, renal diseases, hypothyroidism, Cushing syndrome, or Turner syndrome, as well as obesity with mental retardation, such as Prader-Willi syndrome, Laurence-Moon-Biedl, and Cohen syndrome.

CLINICAL EXAMINATION

The following were performed on all studied groups:

1) Full history taking through clinical examination, with emphasis on any complications or medications;

2) Blood pressure measured according to American Heart Association guidelines;

3) Anthropometric indices: body weight measured to the nearest 0.1 kg with a balance scale and height measured to the nearest 0.1 cm.

Body mass index was calculated as weight divided by height squared (kg/m^2). Waist circumference was measured at the level midway between the lowest rib margin and the iliac crest. Hip circumference was measured at the widest level over the greater trochanters in a standing position by the same examiner; then the waist to hip ratio (WHR) and waist to height ratio (WHTR) were calculated. Percentage body fat (BF %) was calculated by the equation: child BF % = (1.51 × BMI) − (0.70 × age) − (3.6 × gender) + 1.4 where (female = 0 and male = 1) [19].

THE LABORATORY MEASUREMENTS

Five millimetres of venous blood were withdrawn under complete aseptic precautions from fasting subjects (12–14 hours). Pertinent laboratory investigations were performed for all patients and controls including glycosylated haemoglobin (HbA_{1c}) levels, lipid profile (cholesterol, triglyceride, high-density lipoprotein – HDL, and low-density lipoprotein), and liver enzymes including aspartate aminotransferase and alanine aminotransferase

(ALT), using an Olympus AU 400 supplied from Olympus Life and Material Science (Europe GmbH, Wendenstraße, Hamburg, Germany). Viral Markers (HB s Ag, HCV Ab, and HIV Ab) were assessed to exclude viral hepatitis in our cases using the PRECHECK Kit (USA). FBS and lipid profile were assessed using an OLYMPUS AU 400 chemistry analyser. Insulin was estimated by enzyme immunoassay (ELISA).

Insulin resistance was calculated by the homeostasis model (HOMA-IR) using the following formula: HOMA-IR = fasting insulin (mU/l) × fasting glucose (mmol/l)/ 22.5 [4, 9].

Triglyceride-glucose index was calculated with the use of the mathematical formula: natural logarithm – Ln [fasting triglycerides (mg/dl) × FPG (mg/dl)]/2 [9].

The metabolic score for IR (METS-IR) = Ln [(2 × fasting blood glucose (mg/dl) + fasting triglyceride (mg/dl)] × BMI (kg/m^2))/(Ln [HDLc (mg/dl)] [15].

Abdominal ultrasonography was performed, by the same expert, for liver size and echogenicity. Normal liver parenchyma has a homogeneous echotexture with echogenicity equal to or slightly greater than that of the renal cortex and spleen. The liver reveals echogenicity more than the kidney and spleen due to fatty infiltration [20]. Various (0–3) grades of steatosis have been proposed based on analysis of the intensity of the echogenicity [21]. The model of ultrasound apparatus is SA-R3 (No S06YM3 HDC00012F) SAMSUNG MEDISON Company – South Korea.

STATISTICAL ANALYSIS

Each variable was assessed for normal distribution. The standard computer program SPSS for Windows, release 17.0 (SPSS Inc., USA) was used for data entry and analysis. All numeric variables were expressed as mean ± standard deviation. The intergroup comparisons were performed by using an independent-sample t test and a one-way analysis of variance followed by Scheffe's *post hoc* test. Categorical variables are presented as numbers and percentages (%). The 2 groups were compared using the χ^2 test. Pearson's correlation tests (r = correlation coefficient) were used for correlating normal. The potential of the IR indices and NAFLD was examined using receiver operator characteristic (ROC) curve analysis and analysis of variance. For all tests, a probability (P) less than (< 0.05) is considered significant, and $p < 0.01$ was considered highly significant.

STUDY LIMITATIONS

This study is a single-centre cross-sectional study, so these findings need to be further verified by a multicentre prospective cohort study. The small sample size of the included cases led to difficulty in getting solid conclusions. Also, physical activity was not evaluated. Despite these limitations, this study could have important clinical implications.

RESULTS

A total of 190 children were included in our study: 50 normal-weight children, 50 children with overweight, and 90 children with obesity. Our results showed that among the individuals with obesity, 62 (68.9%) were female and 28 (31.1%) were male. Among the individuals with overweight, 27 (54.0%) were female and 23 (46.0%) were male. Among the control individuals, 35 (70.0%) were female and 15 (30.0%) were male. There were no significant statistical differences between groups in terms of age or gender ($p > 0.05$). Descriptive data (clinical, anthropometric, and ultrasonography characteristics and laboratory parameters) of the studied groups are summarised in Tables 1 and 2.

Our data revealed that there were significant statistical differences between them as regards BMI, WHTR, WHR, % body fat, visceral fat thickness (VFT), and liver span ($p = 0.000$). Systolic and diastolic BP levels were significantly higher in overweight and obese children ($p = 0.007$ and 0.003, respectively).

Significantly greater values of HOMA-IR, TyG index, and METS-IR were found in overweight and obese cases ($p = 0.000$). Figure 1 shows the values of METS-IR index in normal weight, overweight, and obese cases.

Role of gender: no differences in VFT, TyG index, and METS-IR were observed between males and females in the 3 groups ($p = 0.484$, 0.430, and 0.940, respectively).

The studied individuals were classified into 2 groups without hepatic steatosis and with hepatic steatosis. The number of hepatic steatosis cases was 37 (19.5%) in all studied children. In children of normal weight only one (2.0%) had hepatic steatosis, in children with overweight 4 (8.0%) had hepatic steatosis, and 32 (90%) of the children with obesity. Hepatic steatosis was significantly higher in boys than girls [22 (59.5%), 15 (40.1%), respectively ($p < 0.001$)]. Table 3 shows the clinical and laboratory characteristics of the groups with hepatic steatosis and without hepatic steatosis. The results showed statistically significant differences in BMI, WHR, BF %, subcutaneous fat thickness, visceral fat, and ALT between the hepatic steatosis group and the group without hepatic steatosis. In our results disregarding ALT, there was a statistically significant difference between cases without hepatic steatosis and cases with hepatic steatosis ($p = 0.013$). There were statistically significant differences in the METS-IR) and the TyG index for NAFLD cases ($p < 0.001$ and < 0.005, respectively).

We found that the TyG index and METS-IR were significantly and positively correlated with HOMA-IR, VFT, fasting insulin, and BMI, ($p = 0.000$). The details are shown in Table 4.

The receiver operating characteristic curve was generated to detect the predictive capabilities of visceral fat,

TABLE 1. Clinical, anthropometric, and ultrasonography characteristics of the studied participants

Items	Group	*n*	Mean	Standard deviation	ANOVA sig.
Age (years)	Normal WT	50	11.69	4.1331	0.065
	Over WT	50	11.44	2.7012	
	Obese	90	12.32	3.1319	
BMI [kg/m^2]	Normal WT	50	19.84	2.99338	0.000
	Over WT	50	28.27	4.63752	
	Obese	90	34.16	4.14195	
WHTR	Normal WT	50	0.466	0.06933	0.000
	Over WT	50	0.471	0.13472	
	Obese	90	0.577	0.13388	
WHR	Normal WT	50	0.839	0.07334	0.000
	Over WT	50	0.693	0.15187	
	Obese	90	0.7750	0.12085	
Systolic blood pressure [mm Hg]	Normal WT	50	102.44	11.114	0.007
	Over WT	50	104.30	11.650	
	Obese	90	108.78	11.449	
Diastolic blood pressure [mm Hg]	Normal WT	50	64.87	7.905	0.003
	Over WT	50	66.60	8.418	
	Obese	90	70.50	10.468	
BF (%)	Normal WT	50	21.610	5.18785	0.000
	Over WT	50	32.635	4.05653	
	Obese	90	38.903	3.14199	
VFT	Normal WT	50	2.6512	0.96666	0.000
	Over WT	50	4.499	1.65195	
	Obese	90	4.6275	1.40276	
SFT	Normal WT	50	1.366	0.65745	0.000
	Over WT	50	1.758	0.52598	
	Obese	90	2.247	0.79656	
Liver span	Normal WT	50	12.342	1.29310	0.000
	Over WT	50	13.568	1.85178	
	Obese	90	14.440	2.01970	

BF% – body fat percentage, BMI – body mass index, SFT – subcutaneous fat thickness, WHR – waist hip ratio, WHTR – waist height ratio, WT – weight, VFT – visceral fat thickness

HOMA-IR, TyG index, and METS-IR for predicting hepatic steatosis (Figure 2). Details of the area under the ROC curve are shown in Table 5.

DISCUSSION

Insulin resistance is an increasing problem due to its association with obesity. To the best of our knowledge, this is the first study to investigate the association between the HOMA-IR, TyG index, and METS-IR insulin resistance indices in obese, normal-weight, and overweight children and adolescents from Egypt. Obese children and adolescents may be at high risk of developing hepatic steatosis if they have insulin resistance. Evidence supports that insulin resistance can cause hepatic steatosis even in individuals who are phenotypically normal weight [2–4].

Concerning hepatic steatosis, it is well known that this disease exhibits age and gender differences in both prevalence and severity. It was significantly higher in boys than girls [22 (59.5%), 15 (40.1%), respectively ($p < 0.001$)]. This result confirms the existence of a gender difference in the prevalence of hepatic steatosis, which has also been

TABLE 2. Laboratory characteristics of the studied participants

Item	Group	*n*	Mean	Standard deviation	ANOVA sig.
HOMA-IR	Normal WT	50	1.7588	0.98543	0.000
	Over WT	50	2.6427	1.91064	
	Obese	90	3.3765	2.02835	
Fasting blood glucose [mg/l]	Normal WT	50	88.3600	8.51592	0.000
	Over WT	50	78.3469	14.98131	
	Obese	90	81.6180	11.02116	
Fasting insulin [mU/l]	Normal WT	50	7.9900	4.39737	0.000
	Over WT	50	14.2021	6.65824	
	Obese	90	17.3920	9.53330	
Cholesterol [mg/m]	Normal WT	50	149.3750	23.38385	0.060
	Over WT	50	165.8511	37.38169	
	Obese	90	162.9770	37.09070	
Triglyceride [mg/ml]	Normal WT	50	91.4500	38.04650	0.221
	Over WT	50	100.7234	30.27749	
	Obese	90	102.8736	35.15739	
HDL [mg/ml]	Normal WT	50	42.2143	19.83411	0.175
	Over WT	50	49.2204	13.77516	
	Obese	90	45.0698	19.25283	
LDL [mg/ml]	Normal WT	50	87.5238	24.44929	0.287
	Over WT	50	95.7306	40.00770	
	Obese	90	97.6177	34.71633	
METS-IR	Normal WT	50	30.4773	5.67504	0.000
	Over WT	50	41.6815	10.01650	
	Obese	90	51.8571	7.72254	
TyG index	Normal WT	50	4.9030	0.47804	0.000
	Over WT	50	5.3354	0.19208	
	Obese	90	5.3838	0.07662	

HDL – high-density lipoprotein, HOMA-IR – the homeostatic model assessment of insulin resistance, LDL – low-density lipoprotein, METS-IR – metabolic score for insulin resistance, WT – weight

shown in previous studies [22–25]. Jeffrey *et al.* and Imanzadeh *et al.* speculate that obese adolescent boys have an increased prevalence of fatty liver compared with obese adolescent girls [22, 23]. Tominaga *et al.* reported that the prevalence of hepatic steatosis was 6.6% in males and 2.0% in females [24], while Gupta *et al.* stated that hepatic steatosis prevalence was 9.8% in girls and 22% in boys [25]. The higher prevalence of hepatic steatosis in boys may be due to excess abdominal fat and the effects of sex hormones.

There have been many hypotheses for the pathogenesis of obesity-associated IR – hyperinsulinaemia and lipotoxicity have been the major concepts. The question of whether insulin resistance or hyperinsulinaemia is the primary disorder of hepatic steatosis in children remains unclear. Our results confirm that there is a strong association between insulin and hepatic steatosis [26, 27]. We found that fasting blood insulin was significantly higher in paediatric hepatic steatosis. Kawasaki *et al.* [28] suggested that hyperinsulinaemia in obese children is the most important predictor of hepatic steatosis.

Our study has shown that significantly greater values of HOMA-IR TyG index were found in overweight and obese cases ($p = 0.000$). The homeostatic model assessment for insulin resistance had a positive correlation with the TyG index ($r = 0.305$, $p < 0.000$); similar correlation rates reported by Locateli *et al.* [29]. The triglyceride-glucose index level has been proposed as an alternative marker for identifying IR, when compared with the (HOMA -IR) index. Furthermore, a recent study provided evidence that an elevated TyG index is associated with

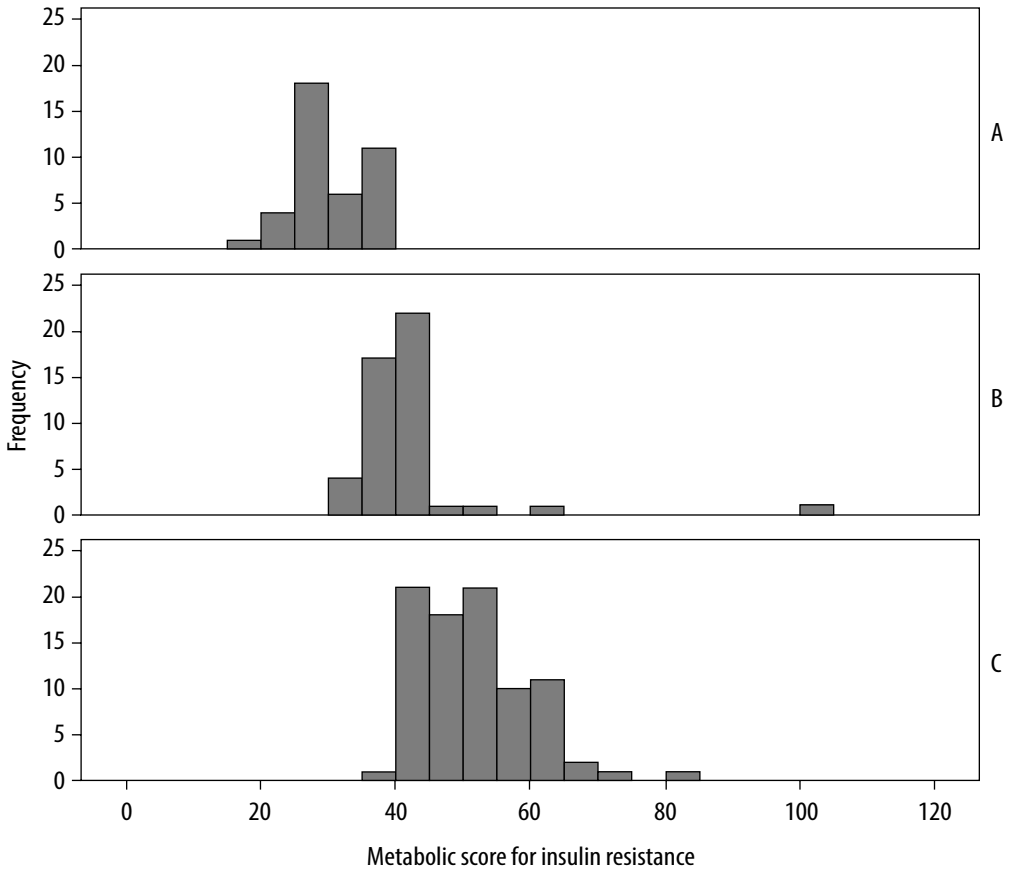

FIGURE 1. The values of metabolic score for insulin resistance index in: A) normal weight, B) overweight, C) obese cases

TABLE 3. Clinical and laboratory characteristics of the groups with and without hepatic steatosis

Characteristics	Without hepatic steatosis ($n = 153$)	With hepatic steatosis ($n = 37$)	
	Mean (SD)	Mean (SD)	*p*-value
BMI [kg/m^2]	27.12 (6.28)	35.97 (5.9.0)	0.001
WHR	0.75 (0.13)	0.8271 (0.09)	0.010
SBP [mm Hg]	104.33 (11.67)	113.11 (11.14)	0.001
DPB [mm Hg]	66.44 (8.86)	74.86 (9.82)	0.001
Fasting insulin	12.95 (8.29)	18.25 (8.64)	0.001
HOMA-IR	2.58 (1.83)	3.44 (1.92)	0.010
AST [U/l 1]	16.77 (3.27)	2 16.27 (3.77)	0.307
ALT [U/l 1]	18.16 (4.00)	2 16.75 (4.04)	0.013
METS-IR	41.16(9.87)	55.49(11.60)	0.001
TyG index	5.22(.34)	5.39(.107)	0.005

ALT – alanine aminotransferase, AST – aspartate transaminase, BMI – body mass index, DPB – diastolic blood pressure, SBP – systolic blood pressure, WHR – waist hip ratio

the presence of cardiovascular risk factors in apparently healthy, normal-weight children and adolescents [30].

The metabolic score for insulin resistance calculation depends on FPG, triglyceride, BMI, and HDL-C, so it can better reflect the metabolic risk of patients with obesity. In this study, we showed that METS-IR is a novel marker for assessing the risk of IR. The metabolic score for insulin resistance is a score that is easy to obtain and calculate in the clinic. Our results indicate that obese children had a significantly higher mean METS-IR level [51.8571 ±7.72254, (p = 0.000)]. Furthermore, correlation with HOMA-IR demonstrated significant positive correlations with METS-IR. (r = 406, p < 0.000). Similar correlation rates have been reported by others [31].

Moreover, hepatic steatosis is expected to become a more serious public health issue because of the increasing prevalence of obesity. Obesity plays a significant role in the development of NAFLD, but the traditional IR indexes did not consider obesity, so they may not be suitable for evaluation in obese people. The metabolic score

TABLE 4. Correlations of metabolic score for insulin resistance and triglyceride-glucose index with other biochemical parameters in the total studied group

Parameters	METS-IR	TyG index	VFT	Fasting insulin	HbA_{1c} (%)	HOMA-IR	BMI
METS-IR							
Pearson correlation	1	0.577*	0.463*	0.451*	0.008	0.406*	0.901*
Sig. (2-tailed)		0.000	0.000	0.000	0.935	0.000	0.000
N	190	190	190	190	190	190	190
TyG index							
Pearson correlation	0.577*	1	0.345*	0.370*	–0.188	0.305*	0.525*
Sig. (2-tailed)	0.000		0.000	0.000	0.054	0.000	0.000
N	190	190	190	190	190	190	190

** Correlation is significant at the 0.01 level (2-tailed).*
BMI – body mass index, METS-IR – metabolic score for insulin resistance, TyG index – triglyceride-glucose, VET – visceral fat thickness

for insulin resistance combined BMI and IR level, on the other hand, in our study demonstrates that METS-IR was the best independent predictor for hepatic steatosis in obese children and adolescents. Similar results were reported by others [31, 32], also in adults [33, 34].

CONCLUSIONS

This study provided evidence that METS-IR is a sensitive marker of IR among obese children and adolescents, and it has a close relationship with hepatic steatosis. The metabolic score for insulin resistance index has significant and positive correlations with HOMA-IR, TyG index, VFT, fasting insulin, and BMI. Children with liver steatosis and elevated liver enzymes are usually asymptomatic, so the screening test for hepatic steatosis among obese children is very important. The metabolic score for insulin resistance could be used by primary care physicians as a screening tool for hepatic steatosis. However, further multicentre prospective cohort studies in children and adolescents with overweight, obesity, as well as normal weight are required to develop cutoff values.

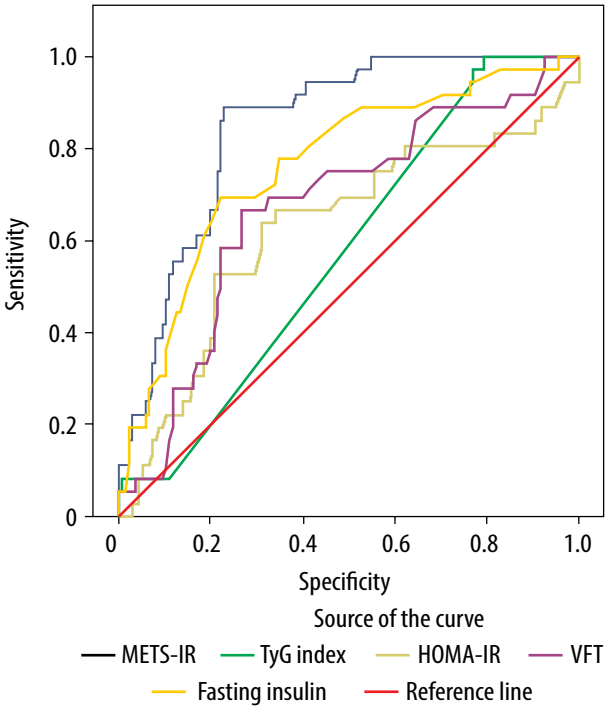

FIGURE 2. Receiver operator characteristic curve

HOMA-IR – homeostatic model assessment for insulin resistance, METS-IR – metabolic score for insulin resistance, TyG – triglyceride-glucose, VFT – visceral fat thickness
Diagonal segments are produced by ties.

DISCLOSURES

1. Institutional review board statement: Not applicable.
2. We would thank the National Research Centre (in-house office for research projects) for the research grants supporting this work. This study was a part of a project No. 10010324. granted by the National Research Centre Egypt.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

TABLE 5. Area under the curve for different test variables

Test result variable (s)	Area	Standard error (a)	Asymptotic sig. (b)	Asymptotic 95% CI Lower pound higher pound	
METS-IR	0.847	0.031	0.000	0.786	0.907
TyG index	0.577	0.048	0.157	0.482	0.671
HOMA-IR	0.625	0.057	0.021	0.513	0.737
Fasting insulin	0.673	0.051	0.001	0.573	0.772
Visceral fat thickness	0.764	0.045	0.000	0.675	0.853

a – under the nonparameteric assumption , b – null hypothesis: true area = 0. 5, HOMA-IR – the homeostatic model assessment of insulin resistance, METS-IR – metabolic score for insulin resistance, TyG index – triglyceride-glucose

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