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Evaluation of indirect indices in the insulin resistance assessment in patients with different body mass index

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ABSTRACT

Introduction: Insulin resistance (IR) is a complex pathophysiological condition with multifactorial etiology characterized by a reduced responsiveness of target tissues to insulin (INS). Indirect indices based on mathematical models and derived from laboratory parameters have become increasingly popular in the past two decades. In this study, we evaluated their ability to predict IR in a population with different body mass index (BMI).

Methods: The matched case–control study was conducted in 2021 and 2022. Secondary data from 129 subjects were obtained from medical records, including demographic characteristics, anthropometric measurements, and biochemical laboratory test results. The studied group consisted of 91 subjects with a suspected diagnosis of IR who were further categorized according to BMI, while control group consisted from 38 age- and gender-matched subjects. Six widely used indirect indices were calculated: Homeostatic Model Assessment for IR (HOMA-IR), quantitative insulin sensitivity check index (QUICKI), McAuley index (MCAi), metabolic score for IR (METS-IR), triglyceride to glucose index (TyG), and TyG to BMI (TyG-BMI).

Results: Significant differences between the subgroups were found in the mean values for HOMA-IR, TyG, TyG-BMI, and METS- IR, while the control group had the highest mean values for the indirect indices QUICKI and MCAi ($p < 0.001$). HOMA-IR, TyG, and TyG-BMI showed statistical significance in predicting IR regardless of BMI ($p < 0.05$). In the obese group, TyG-BMI had good predictive power for discriminating IR (area under the curve [AUC] = 0.820), with a sensitivity and specificity of 84.1% and 87.7%, respectively. HOMA-IR showed moderate predictive power to discriminate IR in the obese group (AUC = 0.720), with a sensitivity and specificity of 70.4% and 89.1%, respectively.

Conclusion: As IR is a multifactorial disease, indirect indices combining laboratory and anthropometric data can significantly help in predicting and mitigating complications.

Keywords: Insulin resistance; homeostatic model assessment for insulin resistance; triglyceride to glucose index; triglyceride to glucose index-body mass index

INTRODUCTION

Insulin resistance (IR) is a complex pathophysiological condition characterized by a reduced responsiveness of insulin target tissues, particularly the liver, skeletal muscle, and adipose tissue, to the metabolic action of insulin (INS) (1). The pathogenesis of IR is multifactorial and involves a complex interplay of genetic predispositions, metabolic disorders, and environmental factors. In particular, oxidative stress, mitochondrial dysfunction, chronic inflammation, and genetic mutations are involved in the disruption of insulin signal transduction pathways. Lifestyle factors such as poor diet, obesity, and insufficient physical activity contribute significantly to the development and exacerbation of IR. Metabolic disorders associated with IR include hyperinsulinemia, impaired suppression of hepatic gluconeogenesis, increased lipolysis in adipocytes, and decreased glucose uptake in muscle tissue, leading to systemic metabolic dysfunction (1-5). In addition, IR is closely associated with a spectrum of health disorders, including visceral obesity, dyslipidemia, endothelial dysfunction, cardiovascular disease, oncogenic processes, polycystic ovary syndrome (PCOS), and non-alcoholic fatty liver disease (3,6). However, the most important complication of IR is type 2 *diabetes mellitus* (T2DM), a condition that contributes significantly to the global burden of disease (7).

While IR has traditionally been associated with the elderly population, recent trends suggest a marked increase in

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prevalence in middle-aged individuals, and this shift is primarily due to increasing rates of obesity and a sedentary lifestyle (6). According to epidemiologic data, IR affects approximately 46.5% of the adult population worldwide, with higher incidence rates in the United States than in European countries (8,9). In addition to age, the influence of gender on the incidence of IR is notably. Studies show that younger men are more frequently affected than women (10). The variability in IR prevalence in different populations can be attributed to differences in the distribution of adipose tissue and the biological effects of sex hormones such as estrogen and testosterone. These elements are important for understanding the pathophysiologic mechanisms underlying IR and for its clinical evaluation and treatment (4,11). The condition is common in women with PCOS and obesity, and around 80% of this subgroup is affected. It is important to emphasize that 30-40% of women with PCOS and normal body weight remain at a Emerging research further highlights a worrying trend in the prevalence of IR in adolescents, including those of normal body weight. This underscores the need for greater awareness and early intervention strategies (10,13).

It is important to recognize that the observed differences in IR prevalence may be due to inconsistent diagnostic criteria worldwide (1,9). Although the hyperinsulinemic clamp technique is the gold standard in diagnostic, it is rarely used in routine clinical practice due to its duration, cost, and complexity (14). Today, various diagnostic approaches incorporate different laboratory parameters. In practice, however, simple indirect indices based on mathematical models are increasingly being used (14,15). Among them, the Homeostatic Model Assessment of IR (HOMA-IR) and the Triglyceride/Glucose Index (TyG) are the most widely used (15). The HOMA-IR calculation includes the fasting INS concentration, whereas the TyG index bypasses the its direct measurement. Therefore, the TyG index is widely used for screening purposes in primary care and valuable for the assessment of dyslipidemia, which plays a role in the development of IR (16). Other indirect indices, the metabolic score for IR (METS-IR), the ratio of TyG to Body Mass Index (TyG-BMI), and measures of insulin sensitivity such as the validated quantitative insulin sensitivity check index (QUICKI) and the McAuley index (MCAi), have been used in numerous research studies to assess IR. When interpreting these indirect indices, threshold values should be considered with the understanding that age, gender, and ethnicity can influence the results (14,17,18). Given the lack of research, this study aims to evaluate the effectiveness of different indirect indices in detecting IR in suspected patients with different body weights.

METHODS

This matched case–control study was conducted between January 2021 and December 2022. Ethical approval was obtained from the Ethics Committee of the Faculty of Health Studies at the University of Sarajevo (number 04-7-17-6/23). Secondary data were obtained from medical records and informed consent from study participants was not required. Personal data were protected and treated confidentially according to the principles of the Declaration of Helsinki.

Data from 129 subjects, including demographic characteristics (age and sex), anthropometric parameters (height and weight), and biochemical laboratory test results were extracted. Of these, 91 with suspected IR and a BMI of more than 25 kg/m^2 were selected for the primary study group. This group was divided into two subgroups based on BMI: overweight (BMI between 25 and 29.9 kg/m^2) and obese (BMI of 30 kg/m^2 or higher). A total of 38 healthy individuals with a BMI of <25 kg/m^2 were matched with the study group based on age and gender and selected as a control group. In addition, the average age of the subjects, rounded to the nearest 5 years, was used for further analysis. The exclusion criteria of the study were age below 18 years, subjects with a confirmed diagnosis of *diabetes mellitus* or PCOS, subjects receiving treatments that could influence the results of the laboratory tests, and subjects with incomplete data sets.

Blood samples were collected from participants after a 12-hour overnight fast, following good laboratory practice protocols. The analytical procedure for the quantification of GLU used the glucose oxidase spectrophotometry method, whereas INS concentrations were determined using a chemiluminescence immunoassay method. The established reference intervals for GLU and INS were 3.9-6.2 mmol/L for GLU and 2.2-25 μIU/mL for INS, respectively, according to the manufacturer's guidelines. For the determination of total cholesterol (TC), high-density lipoproteins (HDL), and triglycerides (TGL), enzymatic methods were used, in particular utilizing the enzymatic activities of cholesterol oxidase-peroxidase, catalase, and glycerol kinase-peroxidase, with measurements performed photometrically. The reference ranges for TC, TGL, and HDL were 3.9-5.2 mmol/L, 0.1-1.7 mmol/L, and 1.15-2.2 mmol/L, respectively. Low-density lipoprotein (LDL) values were calculated using the Friedewald formula (LDL = [TC] – [HDL] – [TGL/5]), with a reference range of 2.6-4.1 mmol/L. The analyzes were performed using Mindray CL-2000i and Mindray BS-480 analyzers, products of Shenzhen Mindray Bio-Medical Electronics Co. from China. To ensure the accuracy and precision of the measurements, commercial control samples from Randox quality controls were included in the analysis at two different concentration levels.

Based on the collected laboratory and anthropometric data, six indirect indices were calculated following the methodology from the study by Romo-Romo et al. (18): HOMA-IR = (Fasting GLU [mmol/L] × Fasting INS [mU/L])/22.5; QUICKI = 1/(Log [Fasting INS (mU/L)] + Log [Fasting GLU (mg/dL)]); MCAi = Exp{2.63 – (0.28 × Ln [Fasting INS (mU/L)]) – (0.31 × Ln [Fasting TGL (mg/dL)])}; METS-IR = [Log((2 × Fasting GLU (mg/dL)) + Fasting TGL (mg/dL)) × BMI (kg/m^2)]/(Log [HDL (mg/dL)]); TyG = Ln (Fasting TGL [mg/dL] × Fasting GLU [mg/dL]/2); and TyG-BMI = TyG index x BMI (kg/m^2).

The statistical analysis was performed using the Statistical Package for the Social Sciences software (version 27.0, IBM Corp., Armonk, NY, USA). Continuous variables were presented as mean (M) and standard deviation, and categorical variables were summarized by their frequency (N) and percentage (%). The normality of the data distribution was assessed using the Kolmogorov–Smirnov test. Non-parametric tests were used for data that did not conform

to a normal distribution. Pearson's Chi-square test was used to compare categorical variables between different groups, whereas the Kruskal–Wallis (KW) test was used for continuous variables. Associations between categorical variables and the different indices were examined by multivariate regression analysis, with odds ratios (OR) and 95% confidence intervals (95%). To assess the diagnostic accuracy of indirect indices in overweight and obese individuals, receiver operating characteristic (ROC) curves were constructed and diagnostic performance was quantified by area under the curve (AUC). $p \leq 0.05$ was considered statistically significant, with the threshold for statistical significance set at 5%.

Data availability

The data sets used and/or analyzed in this study are available on request from the corresponding author.

RESULTS

The baseline characteristics of the study population are presented in Table 1. A total of 129 subjects with a mean age of 34.43 ± 6.71 years were included in the study, the majority of whom were female (n = 103; 79.8%). The largest proportion of study participants was in the overweight group (n = 54; 41.9%), followed by the control group (n = 38; 29.5%) and the obese group (n = 37; 28.7%). Statistically significant differences between the groups were not found regarding gender ($\chi^2 = 1.699$; $p = 0.428$) and age ($\chi^2 = 5.333$; $p = 0.069$).

In Table 2, the levels of the laboratory parameters in the study groups are presented. Both IR subgroups had statistically higher ($p < 0.001$) mean values of GLU (5.334 ± 0.578, 5.422 ± 0.480 mmol/L), TC (5.358 ± 0.731, 5.690 ± 0.678 mmol/L), LDL (3.409 ± 0.743, 3.620 ± 0.630 mmol/L), and TGL (1.690 ± 0.525, 1.975 ± 0.650 mmol/L) than the control group. In addition, INS was significantly higher ($p < 0.001$), twice as high in the overweight subjects (14.722 ± 5.098 μIU/mL) and 3 times as high in the obese subjects (19.311 ± 6.426 μIU/mL) than in the control group (6.679 ± 3.053 μIU/mL). The mean HDL values did not differ significantly between the groups ($p = 0.903$).

Significant differences in HOMA-IR values were found between the groups ($p < 0.001$). The HOMA-IR values were twice as high in the overweight group (3.526 ± 1.423) and 3 times as high in the obese group (4.670 ± 1.637) compared to the control group (1.505 ± 0.736). A similar pattern was found for TyG-BMI ($p < 0.001$). The obese participants had the highest mean values for METS-IR and the TyG index (50.73 ± 13.12 and 5.382 ± 1.881, respectively), while the control group had the highest mean values for the QUICKI (0.369 ± 0.030) and MCAi (8.013 ± 1.212) indices ($p < 0.001$) (Table 3).

The AUC and ROC analyses for six indices are presented in (Table 4; Figure 1A and B). According to the analysis, three indirect indices showed statistical significance in predicting IR regardless of BMI ($p < 0.05$). In the obese group, TyG-BMI had good predictive power for discriminating IR with the highest AUC (0.820), along with the highest sensitivity and specificity (0.841 and 0.877, respectively). In contrast, it had limited discriminatory power in the overweight group, with an AUC of 0.602 and lower sensitivity (0.631) and

TABLE 1. Baseline characteristics of study participants

Variable	IR group				Control group		Total		χ^2	*p*-value
	Overweight		Obese							
	n	%	n	%	n	%	n	%		
Sex										
Male	12	22.2	9	24.3	5	13.2	26	20.2	1.699	0.428
Female	42	77.8	28	75.7	33	86.8	103	79.8		
Age (years)										
<35	25	46.3	17	45.9	26	68.4	68	52.7	5.333	0.069
≥35	29	53.7	20	54.1	12	31.6	61	47.3		

TABLE 2. Laboratory parameters according to the body mass index

Variable	IR group		Control	KW test	*p*-value
	Overweight	Obese			
	Mean±SD [Min - Max]	Mean±SD [Min - Max]	Mean±SD [Min - Max]		
GLU (mmol/L)	5.334±0.578 [4.190-8.010]	5.422±0.480 [4.550-6.360]	4.961±0.249 [4.240-5.430]	22.605	<0.001
INS (μIU/mL)	14.722±5.098 [7.200-34.490]	19.311±6.426 [7.620-31.200]	6.679±3.053 [3.200-17.330]	74.997	<0.001
TC (mmol/L)	5.358±0.731 [3.890-6.830]	5.690±0.678 [4.650-7.310]	4.330±0.952 [3.710-8.190]	44.522	<0.001
HDL (mmol/L)	1.168±0.211 [0.760-1.640]	1.159±0.201 [0.760-1.650]	1.207±0.268 [0.930-1.880]	0.205	0.903
LDL (mmol/L)	3.409±0.743 [1.700-5.700]	3.620±0.630 [2.300-5.000]	2.555±0.830 [1.700-6.000]	34.498	<0.001
TGL (mmol/L)	1.690±0.525 [0.660-3.450]	1.975±0.650 [0.790-3.640]	1.253±0.375 [0.720-2.830]	36.439	<0.001

GLU: Glucose, INS: Insulin; TC: Total cholesterol; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; TGL: Triglycerides, SD: Standard deviation

TABLE 3. Indirect indices values according to the BMI category

Variable	IR group		Control	KW test	*p*-value
	Overweight	Obese			
	Mean±SD [Min-Max]	Mean±SD [Min-Max]	Mean±SD [Min-Max]		
HOMA-IR	3.526±1.423 [1.600-8.900]	4.670±1.637 [1.800-7.700]	1.505±0.736 [0.700-4.100]	38.702	<0.001
METS-IR	46.90±9.44 [30.73-78.12]	50.73±13.12 [30.73-85.80]	44.55±6.94 [34.30-68.27]	27.524	<0.001
TyG	4.531±1.594 [1.756-9.612]	5.382±1.881 [2.046-10.265]	3.114±1.014 [1.778-7.514]	38.281	<0.001
TyG-BMI	124.060±46.366 [49.859-275.890]	172.981±63.144 [65.066-342.844]	73.680±24.044 [41.615-177.322]	57.680	<0.001
QUICKI	0.321±0.015 [0.281-0.354]	0.309±0.016 [0.286-0.349]	0.369±0.030 [0.311-0.408]	76.360	<0.001
MCAi	5.794±0.955 [3.507-8.084]	5.146±0.931 [3.567-7.596]	8.013±1.212 [4.521-9.467]	67.030	<0.001

HOMA-IR: Homeostatic model assessment for insulin resistance, QUICKI: Quantitative insulin sensitivity check index, MCAi: McAuley index, METS-IR: Metabolic score for insulin resistance, TyG: Triglyceride to glucose index, BMI: Body mass index, SD: Standard deviation

TABLE 4. Receiver operating characteristics curve analysis of indirect indices in the detection of insulin resistance in obese and overweight subjects

Group	Variable	AUC [95% CI]	Sensitivity	Specificity	Cutoff	*p*-value
Overweight	HOMA-IR	0.602 [0.505-0.699]	0.631	0.721	2.620490	0.047
	METS	0.396 [0.299-0.493]	0.341	0.491	38.6561	0.428
	TyG-BMI	0.562 [0.461-0.633]	0.611	0.581	77.83518	0.050
	Ty-G	0.584 [0.484-0.684]	0.597	0.594	3.16850	0.049
	QUICKI	0.378 [2.81-0.476]	0.211	0.472	0.30419	0.491
	MCAi	0.384 [0.285-0.482]	0.384	0.612	4.86249	0.474
Obese	HOMA-IR	0.720 [0.633-0.808]	0.704	0.891	2.99510	0.024
	METS	0.330 [0.233-0.428]	0.361	0.451	32.6472	0.472
	TyG-BMI	0.820 [0.737-0.903]	0.841	0.877	123.44868	<0.001
	Ty-G	0.734 [0.636-0.833]	0.769	0.707	3.67293	0.019
	QUICKI	0.172 [0.100-0.244]	0.138	0.197	0.28489	0.681
	MCAi	0.194 [0.144-0.274]	0.241	0.184	3.53703	0.512

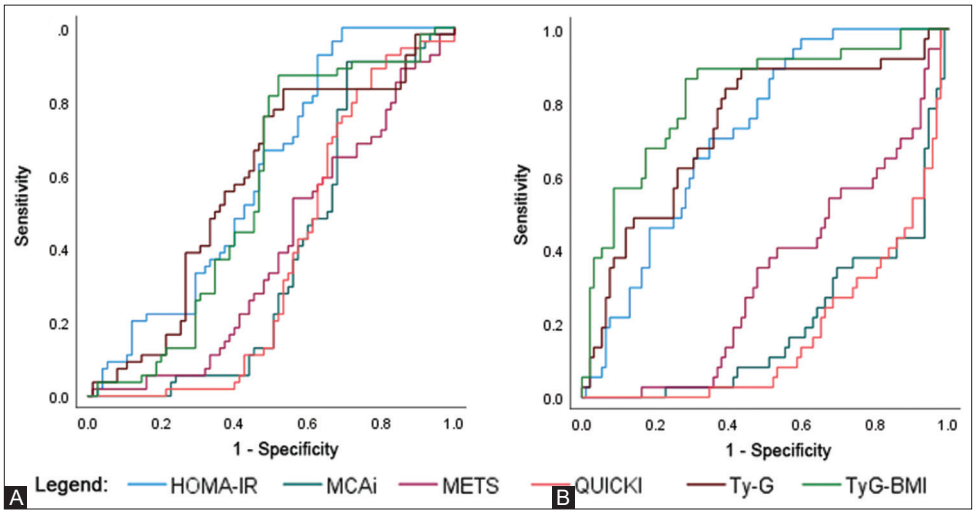

FIGURE 1. (A and B) Receiver operating characteristic (ROC) analysis of indirect indices in the detection of insulin resistance in obese and overweight individuals. (A) ROC analysis of the indices for the overweight group and (B) ROC analysis of the indices for the obese group.

specificity (0.721). TyG showed moderate predictive power in the obese group with an AUC of 0.734, sensitivity of 0.769, and specificity of 0.707, while predictive power was limited in the overweight group. HOMA-IR showed moderate predictive power in the obese group (AUC = 0.720) and limited in the overweight group (AUC = 0.602). Sensitivity and specificity were higher in the obese group (0.704 and 0.891) than in the overweight group (0.631 and 0.721).

DISCUSSION

In the evaluation of IR, various indices are currently in use. However, the literature emphasizes that their applicability may be limited in certain scenarios, requiring cautious interpretation of the results (17). Our study focused on the utility of the six most frequently used indirect indices for the assessment of IR and insulin sensitivity (IS) in different

BMI categories. The mean values of Quicki, MCAi, and METS were higher in individuals with normal BMI than in overweight and obese individuals, and this finding supports their role in the assessment of IS.

For an accurate interpretation of the values of the indirect indices, it is crucial to consider various factors, including age, gender, and BMI. It is noteworthy that women with IR predominated in our study, and our finding is consistent with previous studies by Yilmaz et al. (19) and Benites-Zapata et al. (20). The association between BMI and IR is further highlighted in the study by Horáková et al. (21), which indicates that the risk of developing IR increases significantly with BMI, regardless of age.

We observed statistically significant differences in lipid parameters between overweight and obese subjects, except HDL cholesterol levels. Our results are consistent with a study by Agiues et al. (22) and in contrast to Yilmaz et al. (19). However, the inclusion of these parameters in the assessment of IR could be of great benefit. Dyslipidemia in combination with IR leads to a decrease in HDL cholesterol levels and an increase in TGL and LDL cholesterol levels. This combination impairs the ability of the pancreas to respond appropriately to INS secretion when blood GLU levels are elevated. It is known that dyslipidemia and IR pose a high risk for the development of cardiovascular disease, and the use of effective and accurate indirect indices could potentially help prevent numerous complications associated with metabolic disorders.

In recent years, the HOMA-IR index has shown considerable potential for the assessment of IR in clinical practice. These indices could provide valuable insights into the management and prevention of conditions associated with IR. In a cross-sectional Iranian study conducted by Mohammadabadi et al. (23), the mean value of the HOMA-IR index was 1.9 ± 0.21 in 61 obese women with IR. In contrast, Yilmaz et al. (19), reported a mean HOMA-IR value of 4.52 ± 4.6 in the obese group, with a slightly lower cut-off value of >2.24. Interestingly, a Chinese study with a higher cutoff value of 3.39 reported significantly higher HOMA-IR values of 8.05 ± 7.98 in subjects with T2DM and BMI values below 35 kg/m² (24). In our study, which included predominantly obese women, a mean HOMA-IR index value of 4.670 ± 1.637 was found. Although previous studies have reported a significant advantage of TyG index in the assessment of IR compared to HOMA-IR (23-25), slightly different results were observed in our study with moderate and limited discriminatory power of HOMA-IR in both groups. The variability in the results might be due use of non-standardized cutoff values of the HOMA-IR and TyG index in the assessment of IR. In addition, the observed differences could be result of different sample sizes, metabolic disorders, and the influence of the menstrual cycle on glucose concentration.

Literature data highlight the significant benefit of the TyG index in practice and its potential for application at the primary care level, which is crucial to avoid additional testing. Moreover, this indirect index proves useful in population screening and aids in preventing complications and modifying lifestyle habits that contribute to the worsening of IR (25). In our study, the mean value of the TyG index was higher in obese subjects (5.382 ± 1.881) than in overweight subjects (4.531 ± 1.594). Similar results were reported by Guerrero-Romero et al. (16). The study by Mohammadabadi et al. (23), which included obese women of childbearing age, reported a mean TyG index value of 4.7 ± 0.02, while the study by Luo et al. (24) reported a slightly higher value of 8.11 ± 0.83 in subjects with T2DM. The authors emphasized the importance of using this indirect index due to its ability to assess dyslipidemia in conjunction with the HOMA-IR.

The mean value of the TyG-BMI index was similar to the values obtained by Romo-Romo et al. (18) (172.981 ± 63.144 versus 175.43 ± 18.43), although the subjects included in both categories had lower BMI compared with our results. However, the Taiwanese authors pointed out that the application of this index needs to be adjusted to a specific population due to ethnic characteristics and the influence of the BMI index (26). The influence of the variability of anthropometric parameters on the results of the indirect indices was also shown by METS-IR. The mean value of METS-IR in the study by Widjaj et al. (27), conducted among adolescents with IR was 51.39 ± 9.02, while the values in our study were slightly lower in obese subjects. Nevertheless, it is important to point out that METS-IR showed better results in subjects at risk of developing IR, such as healthy and non-obese subjects, mainly those with normal BMI values (18,27). We support the view that for the diagnosis of IR, which includes indirect indices that use anthropometric values for calculation, it is necessary to consider population characteristics such as the prevalence of obesity, the distribution of muscle and body fat, and dietary habits (22).

In the ROC analysis, TyG-BMI, TyG, and HOMA-IR showed the potential of the indirect indices as indicators of IR in obese individuals, while HOMA-IR showed the greatest potential in the overweight group. The study by Er et al. (26) revealed that the TyG-BMI index with an AUC value of 0.801 had significant utility in assessing IR in non-diabetic individuals. Compared to our study, a slightly higher AUC value of 0.820 (0.737-0.903) was found in the obese group, and this index showed the highest sensitivity of 84.1%. A lower sensitivity of 77.8% was found in the study by Mirr et al. (28), while a higher sensitivity was found in the overweight group. In this study, the TyG index showed the highest sensitivity compared to other indirect indices in obese subjects, indicating the importance of assessing disorders of fat and carbohydrate metabolism in subjects with IR. The study by Mirr et al. (28), recorded a slightly higher AUC value of 0.877 (0.819-0.922), while the study by Luo et al. (24), in a group of subjects with T2DM reported AUC value of 0.785 (0.691-0.879). In the present study, the TyG index showed a slightly lower AUC value of 0.734 (0.636-0.833) in the obese group with high sensitivity and specificity. Compared to the previous parameters, the HOMA-IR demonstrated high sensitivity and specificity in both groups of subjects, justifying its wide application in clinical practice. The AUC value in the obese subjects group was 0.720 (0.633-0.808), and slightly higher results were recorded in the study by Luo et al. (24), with an AUC of 0.73 (0.588-0.873).

CONCLUSION

Given the complexity of IR and its far-reaching impact on public health, a comprehensive and multidisciplinary approach to its understanding, prevention, and management is crucial. The use of indirect indices in practice, based on a combination of laboratory and anthropometric data, can contribute significantly to the prediction and mitigation of numerous complications. Our opinion is supported by the results for TyG-BMI. Considering the increase in the prevalence of IR at a global level, it is necessary to conduct larger studies to establish cutoff values for a specific region.

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DECLARATION OF INTEREST

Authors declare no conflicts of interest.

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