



RESEARCH ARTICLE

Optimal cutoff for the evaluation of insulin resistance through triglyceride-glucose index: A cross-sectional study in a Venezuelan population [version 1; referees: 1 approved]

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Abstract

Background: Insulin resistance (IR) evaluation is a fundamental goal in clinical and epidemiological research. However, the most widely used methods are difficult to apply to populations with low incomes. The triglyceride-glucose index (TGI) emerges as an alternative to use in daily clinical practice. Therefore the objective of this study was to determine an optimal cutoff point for the TGI in an adult population from Maracaibo, Venezuela.

Methods: This is a sub-study of Maracaibo City Metabolic Syndrome Prevalence Study, a descriptive, cross-sectional study with random and multi-stage sampling. For this analysis, 2004 individuals of both genders ≥18 years old with basal insulin determination and triglycerides < 500 mg/dl were evaluated.. A reference population was selected according to clinical and metabolic criteria to plot ROC Curves specific for gender and age groups to determine the optimal cutoff point according to sensitivity and specificity. The TGI was calculated according to the equation: $\ln \left[\frac{\text{Fasting triglyceride (mg / dl)} \times \text{Fasting glucose (mg / dl)}}{2} \right]$.

Results: The TGI in the general population was 4.6 ± 0.3 (male: 4.66 ± 0.34 vs. female: 4.56 ± 0.33 , $p = 8.93 \times 10^{-10}$). The optimal cutoff point was 4.49, with a sensitivity of 82.6% and specificity of 82.1% (AUC=0.889, 95% CI: 0.854-0.924). There were no significant differences in the predictive capacity of the index when evaluated according to gender and age groups. Those individuals with $TGI \geq 4.5$ had higher HOMA2-IR averages than those with $TGI < 4.5$ (2.48 vs 1.74, respectively, $p < 0.001$).

Conclusions: The TGI is a measure of interest to identify IR in the general population. We propose a single cutoff point of 4.5 to classify individuals with IR. Future studies should evaluate the predictive capacity of this index to determine atypical metabolic phenotypes, type 2 diabetes mellitus and even cardiovascular risk in our population.

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report

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Abbreviations

Free Fatty Acids (FFA); Area under curve (AUC); Type 2 diabetes mellitus (DM2); Cardiovascular disease (CVD); Distance to ROC (DtR); Fasting Glucose (FG); Homeostasis Model Assessment (HOMA-IR); Insulin resistance (IR); Youden Index (J), Metabolic Syndrome (MS); Triglyceride (TAG); Triglyceride - Glucose index (TGI)

Introduction

Insulin resistance (IR) is a metabolic condition in which insulin-dependent tissues become less sensitive to insulin action, leading to an imbalance in the metabolism of carbohydrates, lipids and proteins¹. This condition is caused by the influence of different risk factors in the population, such as aging, alcohol consumption, smoking, hypercaloric diets, sedentary lifestyle and obesity². Its role in the development of different pathologies, as cardiovascular disease (CVD)³ and cerebrovascular disease⁴, is now recognized, as well as playing an important role in the pathogenesis and clinical outcomes of the metabolic syndrome (MS)⁵ and type 2 diabetes mellitus (DM2)⁶.

In 1963, Randle and colleagues were among the first to investigate the pathophysiology of IR⁷, suggesting the elevation of free fatty acids (FFA) in the splenic circulation as the cornerstone of this disorder. They proposed the glucose fatty acid cycle, called the Randle cycle. Years later, a theory proposed by Shulman⁸ surfaced, which continued to support the role of FFA in the pathophysiology of IR. However, these authors suggested that FFA and its products, such as diacylglycerol, acyl-coA and ceramides, activate serine-threonine kinases, which phosphorylate important proteins, inhibit the insulin signaling pathway and subsequently translocated glucose transporter 4 (GLUT4) to the plasma membrane⁸.

Although many aspects remain to be clarified in the pathophysiology of IR, its long-term complications have generated great interest in the determination of ideal methods that allow the promotion of an early and accurate diagnosis in risky populations⁹. In this sense, the Euglycemic-Hyperinsulinemic Clamp is considered the gold standard for the determination of IR¹⁰, but the high cost and impracticability of this method has promoted the development of new techniques for the estimation of insulin sensitivity. Many mathematical models have been proposed in recent years with the objective of simplifying the measurement of IR¹¹, highlighting the Homeostasis Model Assessment (HOMA-IR), a validated method to measure IR from serum glucose and fasting serum insulin¹². This index has been studied in our population, which was conducted in 2026 subjects and evaluated the factors related to insulin resistance (defined as $HOMA2-IR=2$)¹³. However, one of the biggest limitations is the lack of accessibility to populations with lower incomes, since all the individuals require blood work to calculate the serum insulin.

Simental-Mendia *et al.*^{14,15} have proposed and validated a new formula to evaluate IR from the levels of serum triglycerides (TAG) and fasting glucose (FG), which is known as 'Triglyceride/Glucose Index' (TGI), this formula is a potential diagnostic tool when other

standard methods are not available. Based on the information above, the objective of the study is to determine an optimal cut point of the TGI to determine IR and to evaluate the behavior according to the main sociodemographic characteristics in an adult population from Maracaibo, Zulia, Venezuela.

Methods

Sample selection and study design

The Maracaibo City Metabolic Syndrome Prevalence Study (MMSPS) study is a descriptive, cross-sectional, randomized, multi-stage sampling study that was carried out in Maracaibo-Venezuela; the second most populated city in the country with an approximate population of 2,500,000, in order to evaluate the cardiovascular and metabolic risk factors of this locality, during the period May 2007 - December 2009¹⁶. The only inclusion criteria was individuals older than 18 years. The sample (1,986 individuals) was calculated based on the estimates of the population in the city given by the National Institute of Statistics (1,428,043 inhabitants for 2007). A total of 244 individuals (12%) were added through oversampling, in order to increase the accuracy of the estimates obtained from the smaller subgroups of the sample, representing a total of 2230 individuals of both genders. Sampling details have been previously published¹⁶. The study was approved by the Bioethics Committee of the Endocrine and Metabolic Research Center – University of Zulia (approval number: BEC-006-0305). This ethical approval included all future studies that used the data from the MMSPS. All participants signed written consent before being questioned and physically examined by a trained team.

For this analysis, 2004 individuals were selected according to the availability of baseline insulin, in addition to the exclusion of individuals with TAG ≥ 500 mg/dl. Based on this sub-sample, a reference population was selected based on the following criteria: abdominal obesity, total cholesterol, high blood pressure and personal history of DM2, coronary artery diseases, cardiac arrhythmias, acute cerebrovascular disease, and polycystic ovaries; with the purpose of establishing a subsample of healthy and sick subjects without using definitions or diagnostic criteria that include TAG and glycaemia values to avoid variables correlation *a priori* (Figure 1).

Individual evaluation

The data was gathered through a complete medical history performed by the trained team: the past medical and family history for cardiovascular and endocrine-metabolic diseases was assessed.

Blood pressure and anthropometric evaluation

The auscultation method was used for the measurement of blood pressure, using stethoscopes and calibrated sphygmomanometers adequately validated. The procedure was performed with the individual at rest (at least 15 minutes) and sitting with both feet on the floor; three measurements were taken, with 15 minutes of separation between one measurement and the other. Systolic blood pressure was determined by auscultation of the first Korotkoff noise, while diastolic blood pressure was determined on auscultation of the fifth Korotkoff noise.

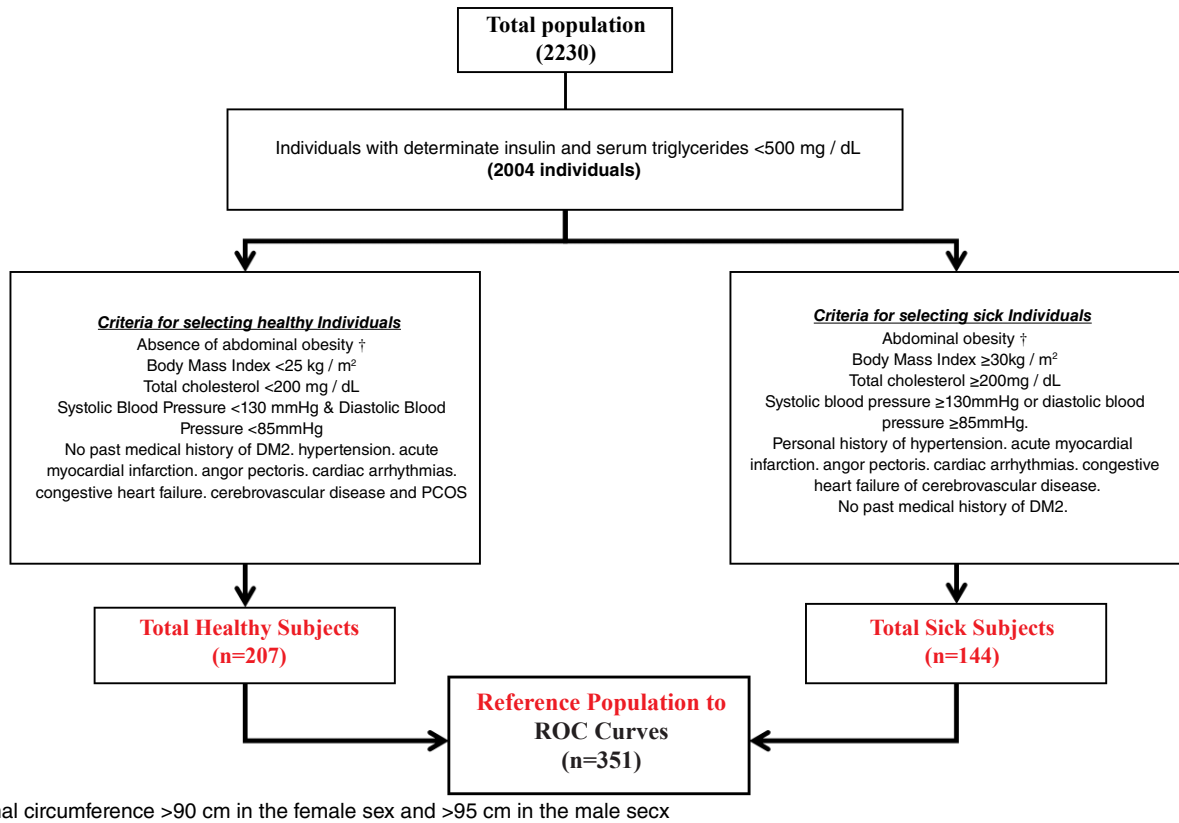


Figure 1. Diagram of reference population selection for cut-off points determination of the triglyceride-glucose index in Maracaibo city, Venezuela. ROC Curves: Receiver operating characteristic curves.

Weight was determined through a dielectric balance (Tanita, TBF-310 GS Body Composition Analyzer, Tokyo, Japan), and height was obtained by using vertical tape calibrated in centimeters and millimeters. Individuals were standing and barefoot, with light clothing throughout the evaluation, maintaining a straight posture and head up. Body Mass Index was calculated using the weight/height formula and classified according to the criteria proposed by the World Health Organisation (low weight, normal weight, overweight, Obesity type I, II and III)¹⁷. The measurement of the abdominal circumference was taken with a plastic metric tape in centimeters at equidistant points between the costal ridge and the iliac crest, according to the protocol proposed by the National Salute Institute of the United States¹⁸. Abdominal obesity was defined according to specific cutoff points for our previously determined population, ≥ 90 cm in women and ≥ 95 cm in men¹⁹.

Laboratory analysis

Overnight fasting determination of glucose, total cholesterol, triglycerides, and HDL-C was done with an automated analyzer (Human Gesellschaft für Biochemica und Diagnostica mbH,

Germany). The intra-assay variation coefficient for total cholesterol, TAG, and HDL-C was 3%, 5%, and 5%, respectively. Insulin was determined using an ultrasensitive ELISA double-sandwich method (DRG Instruments GmbH, Germany, Inc.), with a Detection Limit <1 mU/L. The HOMA2IR index was calculated using the software administered by the Oxford Diabetes Center, Endocrinology and Metabolism (available at <http://www.dtu.ox.ac.uk/homacalculator/index.php>). A cutoff value of ≥ 2 was used to determine IR²⁰.

Calculation of TGI

The calculation of the TGI was done using the equation: $\ln [Fasting TAG (mg/dl) \times FG (mg/dl)]/2$; thus being expressed on a logarithmic scale^{14,21}.

Statistical analysis

Qualitative variables were expressed in absolute and relative frequencies. While the quantitative variables were expressed as arithmetic mean \pm SD, with the previous analysis of normality through means of a Geary test. Significant differences between groups were assessed using the Student's *t*-test, while an ANOVA

was used for comparisons between three or more groups. Data were analyzed through the SPSS v.21 for Windows (IBM Chicago, IL), considering statistically significant results when $p < 0.05$.

ROC curves were plotted in the reference population (Figure 1) to analyze the predictive capacity and to determine an optimal cutoff point for the TGI. ROC curves were gender-specific using R version 3.4.1. Several indexes were calculated to evaluate the optimum cutoff point in the curve. The area under the curve (AUC) is used to establish the ability of the test to obtain an appropriate cutoff where an AUC of 1.00 is considered a perfect diagnostic test²². Comparisons between AUC were performed using Delong's test²³. The Youden Index (J) was calculated using the formula $[J = \text{sensitivity} + \text{specificity} - 1 = S - (1 - Es)]^{23}$, obtaining the value of true positives (sensitivity) and false positives (1-specificity) when $J > 1$. The minimum cutoff point was calculated using the nearest point to 0.1 in the ROC curves formula: square root of $[(1 - \text{sensitivity})^2 + (1 - \text{specificity})^2]^{24}$. In addition, probability radius

positive $[\text{sensitivity}/(1 - \text{specificity})]$ and negative $[(1 - \text{sensitivity})/\text{specificity}]$ were calculated to aid in the selection of the cutoff point together with the Youden index. Likelihood values > 1 indicate association with the disease, while those < 1 indicate association with the absence of the disease²⁵.

Results

General characteristics of the sample

A total of 2004 individuals were studied, 53.4% ($n = 1050$) were female, the mean age of the population was 39.6 ± 15.3 . The general characteristics of the population are shown in Table 1. The mean TGI in the general population was 4.6 ± 0.3 , with higher values in males (males: 4.66 ± 0.34 vs. females: 4.56 ± 0.33 , $p = 8.93 \times 10^{-10}$). The epidemiological behavior of the TGI according to age and ethnicity is shown in Table 2, which shows an increase of the index as age increases. In regards to ethnicity, no statistically significant differences were found between means ($p = 0.326$).

Table 1. General characteristics of the sample studied, Maracaibo city, Venezuela.

	Female (n= 1050)		Male (n= 954)		Total (n=2004)	
	n	%	n	%	n	%
Age (years)						
<30	308	29.3	363	38.1	671	33.5
30–49	420	40.0	350	36.7	770	38.4
≥ 50	322	30.7	241	25.3	563	28.1
Ethnicity						
Mixed	794	75.6	740	77.6	1534	76.5
White Hispanic	171	16.3	145	15.2	316	15.8
Afro-Venezuelan	27	2.6	32	3.4	59	2.9
American Indian	47	4.5	36	3.8	83	4.1
Other*	11	1.0	1	0.1	12	0.6
Triglycerides (mg/dl)						
<150	815	77.6	644	67.5	1459	72.8
≥ 150	235	22.4	310	32.5	545	27.2
Glycaemic status[†]						
Euglycemic	774	73.9	662	69.4	1436	71.7
Impaired fasting glucose	186	17.7	212	22.2	398	19.9
Type 2 diabetes mellitus	88	8.4	80	8.4	168	8.4

*Asian and Arabic descent.

[†]Criteria according to the ADA 2016 consensus

Table 2. Epidemiological behavior of the triglyceride-glucose index in the general population according to sociodemographic variables, in Maracaibo city, Venezuela.

	TOTAL (n=2004)	
	Mean±SD	p*
Gender		8.93×10 ⁻¹⁰
Female	4.56±0.33	
Male	4.66±0.34	
Age (years)		6.21×10 ⁻⁷⁷
<30	4.43±0.28	
30–49	4.65±0.33	
≥50	4.77±0.31	
Ethnicity		0.326
Mixed	4.60±0.33	
White Hispanic	4.62±0.35	
Afro-Venezuelan	4.68±0.32	
American Indian	4.60±0.31	
Other [†]	4.51±0.28	

*Student's *t*-test (for more than two groups one-way ANOVA was used).

[†]Asian and Arabic descent.

SD: standard deviation

Post-hoc Tukey: <30 years vs 30–49 years, p=5.09×10⁻⁹; <30 years vs ≥50 years, p=5.09×10⁻⁹; 30–49 years vs ≥50 years, p=5.10×10⁻⁹.

Table 3. Epidemiological behavior of the triglyceride-glucose index in the reference population according to sociodemographic variables, in Maracaibo city, Venezuela.

	TOTAL (n=351)		
	n	Mean±SD	p*
Gender			5.83-10 ⁻⁶
Female	190	4.41±0.29	
Male	161	4.56±0.32	
Age (years)			8.42×10 ⁻²⁸
<30	178	4.31±0.29	
30–49	118	4.61±0.31	
≥50	55	4.72±0.23	
Ethnicity			0.413
Mixed	268	4.48±0.32	
White Hispanic	52	4.48±0.34	
Afro-Venezuelan	8	4.59±0.26	
American Indian	20	4.39±0.23	
Other [†]	3	4.25±0.26	

*Student's *t*-test (for more than two groups one way-ANOVA was used).

[†]Asian and Arabic descent.

SD: Standard deviation.

Post-hoc Tukey: <30 years vs 30–49 years, p=5.09×10⁻⁹; <30 years vs ≥50 years, p=5.09×10⁻⁹; 30–49 years vs ≥50 years, p=0.03.

When assessing the reference population (n=351); healthy: n=207 – sick: n=144, a similar behavior of the TGI was found according to age and ethnicity (Table 3). In addition, there were no differences in TGI mean between the general and reference population.

Cutoff points for the TGI in the general population by gender

For the determination of cutoff points of the TGI, ROC curves were plotted for the general population by gender (Figure 2). An AUC of 0.889 (95% CI: 0.854-0.924) was obtained for the general population with a proposed cutoff of 4.49 (82.6% sensitivity, and 82.1% specificity), while the AUC calculated for males was 0.903 (95% CI: 0.856-0.950) and for females was 0.871 (95% CI: 0.818-0.925); Delong's test: p=0.37. The cutoff points and index calculated according to the ROC curves are shown in Table 4.

Cutoff points for the TGI in the general population by age

When assessing the predictive capacity of the TGI according to age, a higher AUC was obtained in individuals between the ages of 30 and 50 years old (AUC=0.876; 95% CI: 0.812-0.939); however, when comparing AUCs among age groups, no significant

differences were found. The cutoff points and index calculated according to age are shown in Table 5, which are similar to that proposed for the general population (<30 years: 4.48 [65.0% sensitivity, and 84.8% specificity]; 30–50 years: 4.51 [84.7% sensitivity, and 78.3% specificity], ≥50 years, 4.51 [86.5% sensitivity, and 66.7% specificity]).

HOMA2IR according to cutoff points of the TGI

Finally, when assessing HOMA2-IR levels according to the proposed cutoff point of the TGI for the general population (Figure 3), individuals with TGI≥4.5 exhibited higher levels of HOMA2IR than those who had a TGI <4.5 (2.48 vs 1.74, respectively, p<0.001), with similar behavior by gender.

Dataset 1. Data for the study 'Optimal cutoff for the evaluation of insulin resistance through triglyceride-glucose index: A cross-sectional study in a Venezuelan population'

<http://dx.doi.org/10.5256/f1000research.12170.d171840>

This data is available in both .SAV and .xls forms. BMI: Body Mass Index; BP: Blood Pressure.

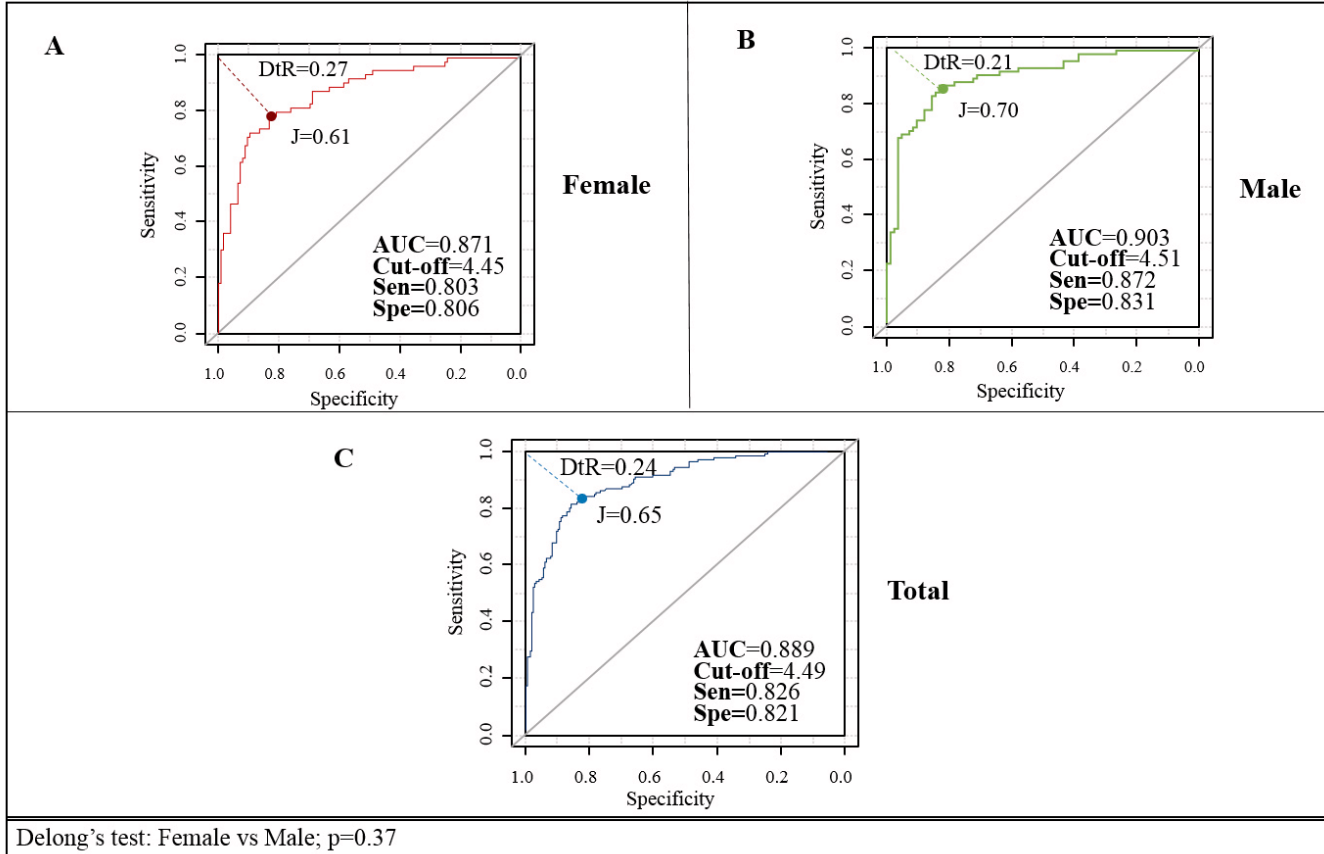


Figure 2. Receiver Operating Characteristic curves for the triglyceride-glucose index in the general population by gender, in Maracaibo city, Venezuela. DtR, Distance to ROC; J, Youden Index; AUC, are under the curve; sen, sensitivity; spe, specificity.

Table 4. Cut-off points for triglyceride-glucose index (TGI) selected in the general population and by gender, in Maracaibo city, Venezuela.

Gender	TGI [†]	Sensitivity (%)	Specificity (%)	Youden index	ROC distance	LR+	AUC (95%CI)
Female	4.45	80.3	80.6	0.61	0.276	4.14	0.871 (0.818–0.925)
Male	4.51	87.2	83.1	0.70	0.212	5.15	0.903 (0.856–0.950)
Total	4.49	82.6	82.1	0.65	0.249	4.61	0.889 (0.854–0.924)

[†]Cut-off points selected according to the best combination of indexes. Delong's test= 0.37

Table 5. Cut-off points for triglyceride-glucose index (TGI) selected according to age groups, in Maracaibo city, Venezuela.

Age (years)	TGI [†]	Sensitivity (%)	Specificity (%)	Youden index	ROC distance	LR+	AUC (95%CI)
<30	4.49	65.0	84.8	0.50	0.381	4.27	0.789 (0.684–0.895)
30–50	4.51	84.7	78.3	0.63	0.265	3.89	0.876 (0.812–0.939)
≥50	4.51	86.5	66.7	0.53	0.359	2.59	0.776 (0.602–0.949)

[†]Cut-off points selected according to the best combination of indexes

Delong's test: <30 vs 30–50 years; p=0.171. <30 vs >50 years; p=0.885. 30-50 vs >50 years; p=0.34.

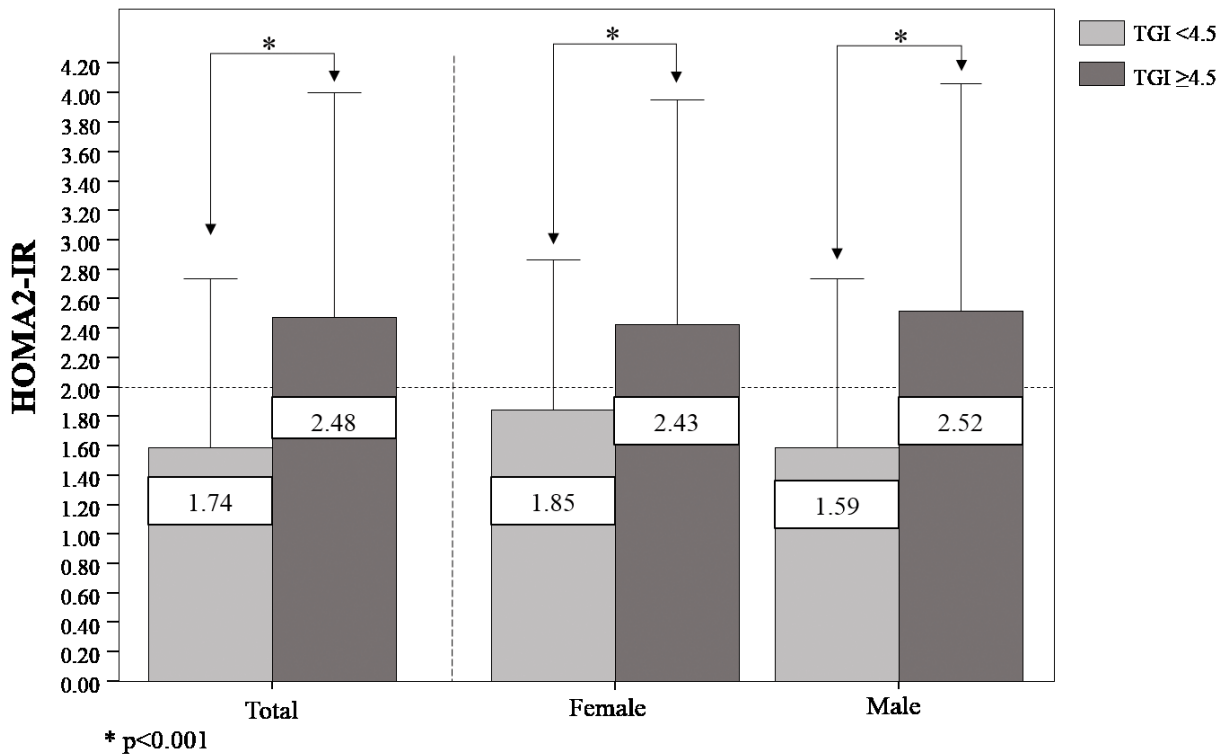


Figure 3. HOMA2-IR levels according to the specific cut-off point for the triglyceride-glucose index in the general population, in Maracaibo city, Venezuela.

Discussion

The evaluation of IR is an objective that continues to acquire relevance in clinical and epidemiological research, due to the potential role of this disorder in the pathophysiology of MS²⁶, the consequent risk of developing DM2²⁷ and CVD²⁸. In developing countries with economic difficulties in health systems, such as Venezuela, routine measurements of plasma insulin are not easily accessible, which forces the use of other indexes based on the role of glucolipototoxicity as a key element in the development of IR²⁹. In this way, the TGI has recently been proposed and validated as a useful alternative in clinical settings, and has been well accepted due to the high predictive power observed with respect to other indices³⁰.

Several studies have shown that the TGI better predicts HOMA-IR levels than variables, such as the TAG/HDL index, visceral adiposity index, leptin, Apo-B/Apo-AI, and lipid parameters^{29,30}, representing a very good correspondence with this index³¹, which constitutes an important tool with high validity for the clinician when facing limited access to lab work-ups. However, in view of the wide variability of TAG levels according to the ethnic, sociocultural and genetic characteristics of each population, the need arises to evaluate their epidemiological behavior and establish reference values specific to each region.

In regards to our study, the mean TGI was higher in men compared to women. Several studies have reported similar findings^{14,32}; however, when plotted ROC curves for the TGI for each gender, significant differences in the AUC values by gender were not observed. We propose the use of a single cutoff point of 4.5 for the identification of sick individuals in the clinical practice as an easy tool for the clinician.

These findings corresponded to those originally reported by the index's authors in 2010¹⁵, when evaluating the discriminative ability of this index to determine IR against the euglycemic-hyperinsulinemic clamp in a population of 99 individuals (11 healthy, 34 obese, 22 with prediabetes and 32 with DM2) suggesting a cutoff point of 4.68 with high sensitivity (96.5%) and specificity (85.0%). Based on these findings, several studies have attempted to establish specific cutoff points for their populations, assessing the clinical utility of this index. In 2011, in a Brazilian population, Vasques *et al.*³³ stipulated that the TGI had a slightly better performance to diagnose IR compared to HOMA2-IR (AUC=0.79 vs AUC=0.77, respectively). Although these investigators did not perform any statistical tests to compare the diagnostic capacity between both indices, the similar behavior allows the use of TGI in clinical settings routinely.

On the other hand, Unger *et al.*²¹ conducted a cross-sectional study in an Argentinean population with the aim of evaluating the discriminative capacity of the TGI for the diagnosis of MS, taking into account that the development of this syndrome is related to IR. They set a cutoff point of 8.8 (sensitivity = 79%, specificity = 86%)

to diagnose MS in their population, a value that differs markedly from the values in our region and those originally proposed. These differences have been observed in other studies³⁴⁻³⁶, so considering that the means of TAG do not vary significantly between these and our study, this discrepancy could be attributable to errors in the calculation of the original formula³⁷.

In regards to age, an increase in the average TGI was observed as age increased, similar to that found by Navarro-González *et al.*³⁸ and Cuda *et al.*³⁹. This can be associated with the increase in oxidative stress inherent to aging, which would favor the development of IR, as well as the elevation of plasma levels of TAG⁴⁰. In this sense, Guerrero-Romero *et al.*³¹ recently evaluated the performance of the TGI to determine IR against the euglycemic-hyperinsulinemic clamp in a young Mexican adult population (mean age: 19.2±1.4), with the goal of establishing a specific cutoff point in this population. However, the cutoff points of 4.55 in men and 4.68 in women were similar to the value proposed previously for the general population, and similar to the one proposed in our study. Also, when we plotted ROC curves for each age group, we did not observe significant differences between AUC, ruling out the need to establish age-specific cutoff points.

In relation to ethnicity, the small sample in each of the categories precludes the generalization of these results, but it shows that it is necessary to evaluate the behavior of the TGI in the different ethnic groups on a large scale and to determine if there are significant differences between them because there is no data reported on this diagnostic method among various ethnicities.

Based on previous analyzes, the usefulness of the TGI has been extended in several regions of the world, being also used in the screening of other pathological metabolic states in which the IR underlies the fundamental pathophysiological mechanism, such as DM2⁴¹ and atypical metabolic phenotypes^{42,43}. In fact, the TGI appears to be a better predictor of incidence of DM2 than TAG³⁸, weight gain⁴³ and other IR indices, such as TAG/HDL and HOMA-IR⁴¹. Moreover, Lee *et al.* performed a retrospective study involving 2900 Korean non-diabetic adults determinate as a cutoff point 8, (AUC=0.751, 95% CI 0.704-0.799) to predict the incidence of DM2 in their population. In addition, only individuals with a TGI >8.8 were associated with a significant risk of DM2 incidence, regardless of the presence of obesity⁴⁴.

Additionally, the index can better predict the patient's metabolic status, as it has been shown in discriminating atypical metabolic phenotypes, such as metabolically obese normal weight and healthy obese, as well as their progression throughout time³⁵. Cutoff points have been determined to discriminate these pathological metabolic status in two populations of Korea^{34,35}, which could facilitate the definition of these phenotypes. Future studies in our population should evaluate the utility of this index in the identification of these abnormal pathological statuses. It is important to mention that within the limitations of this study it is necessary to consider the

transversal design and the lack of gold standard during the process of selection of the reference population.

Conclusions

The TGI is an instrument of interest when it comes to identifying IR in the general population. We propose a single cutoff point of 4.5 to identify patients with IR, as we identify the need for generalization of the formula calculation in order to be able to adequately compare the differences observed in various studies. Despite this, due to the easier application in clinical practice, future studies in our population should evaluate the predictive capacity of this index to determine atypical metabolic phenotypes, DM2 and CVD risk.

Data availability

Dataset 1: Data for the study 'Optimal cutoff for the evaluation of insulin resistance through triglyceride-glucose index: A

cross-sectional study in a Venezuelan population'. This data is available in both .SAV and .xls forms. BMI: Body Mass Index; BP: Blood Pressure. doi, [10.5256/f1000research.12170.d171840](https://doi.org/10.5256/f1000research.12170.d171840)⁴⁵

Competing interests

No competing interests were disclosed.

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This research article deals with an interesting subject related to insulin resistance, its evaluation without the need of an insulin blood test. We believe that it can contribute to identify patients with metabolic risk. Authors have clearly elaborated the background of the problem and current literature is cited. The study is properly conducted and described. But, there are some shortcomings that should be corrected:

- Abstract: Line 1, there are two dots after the word *evaluated*.
- Keywords are absent.
- Abbreviations: Page 3, we considered unnecessary this subtitle because the abbreviations are spelled out in the text.
- Sample selection and study design: We have interpreted that the presence of all the cited criteria was necessary to classify an individual in the reference population, but it is not clear in the text. Authors should explain how many of the cited criteria were considered to classify an individual as healthy or sick.
- Figure 1: Authors should consider the previous correction also in this figure. Authors should replace the explanation [†]*Abdominal circumference > 90 cm in the female sex and > 95 cm in the male sex* with [†]*Abdominal obesity defined as: abdominal circumference > 90 cm in the female sex and > 95 cm in the male sex*. Authors should highlight in the respective box that the population of 2004 individuals is the General population.
- Laboratory analysis: If possible, authors should provide the fasting time in hours owing the lack of harmonization in this preanalytical aspect worldwide. Glucose and insulin analytical coefficients of variation should be provided. It is not necessary HDL-C description as this analyte was not used in the present research.
- Statistical analysis: Authors should verify the ROC curve formula described to calculate the minimum cutoff point.
- Results: Authors should correct the second subtitle because the cutoff points were calculated in the reference population (n=351) – as stated in Methods – and not in the general population (n=2004); also in the second line of the respective text. Authors should correct the third subtitle

because the cutoff points were calculated in the reference population (n=351) – as stated in Methods – and not in the general population (n= 2004); authors should clarify the comparison made in line 7 of the respective text, we understand that they are comparing the cutoff values obtained by age with the cutoff value obtained for the total reference population.

- Table 2: Authors should replace the word *TOTAL* with *TGI* so as to allow a better interpretation of the values shown in the table. Also the number of individuals should be described by variable, as in Table 3.
- Table 3: Authors should replace the word *TOTAL* with *TGI* so as to allow a better interpretation of the values shown in the table.
- Table 4: Authors should correct the table title because the cutoff points were calculated in the reference population (n=351) – as stated in Methods – and not in the general population (n= 2004).
- Table 5: Authors should indicate in the title that the cutoff points were calculated in the reference population (n= 351),as in the other tables.
- Figure 2: Authors should correct the title because the cutoff points were calculated in the reference population (n=351) – as stated in Methods – and not in the general population (n= 2004).
- Figures and tables in general: Authors should verify that each figure or table has a concise title of no more than 15 words. Authors should provide a legend for each figure and table that briefly describes the key points and explain any symbols and abbreviations used. Also the *n* value should be provided in each table and figure to help reader's interpretation.
- Discussion: Authors states that TGI was higher in men compared to women, and that an increase in its average value was observed as age increased. It would be interesting to evaluate the effect size of these statistical differences so as to interpret the clinical importance of these increases;Cohen'sd–<https://www.uccs.edu/~lbecker/>– can be used for this purpose if the variable has a parametric distribution.
- General considerations: Authors should express *p* values with three decimals in all the text, tables and figures. The word *cutoff* is written as *cut-off* in some parts of the text, figures and tables, the same happens with the word *indexes* and *indices*. They should be written in the same way in all the text. It would be advisable to replace in the introduction: *blood work to calculate the serum insulin* with *insulinblood test*; in all the text: *sick* with *unhealthy*; in the conclusions: *generalization* with *harmonization or standardization*.

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

We have read this submission. We believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reader Comment 20 Oct 2017

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The Editorial Team can confirm that keywords are included in the article, but only in the article's metadata rather than being displayed on the Article Page or part of the PDF.

Competing Interests: No competing interests were disclosed.
