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Original Article

Diagnostic accuracy of triglyceride/glucose and triglyceride/HDL index as predictors for insulin resistance in children with and without obesity

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ABSTRACT

Objective: To investigate which of two indexes (TyG or TG/HDL) are the best predictors for insulin resistance (IR) and to evaluate the magnitude of each cardiometabolic risk factor in Mexican schoolchildren of 5–9 years with overweight-obesity and normal weight.
Material and methods: We realized a comparative cross-sectional prospective study in accordance of STARD guidelines. Setting was Family Medicine Unit (FMU) No. 80 of Mexican Institute of Social Security(IMSS) of Morelia, Michoacán, Mexico. Children between 5 and 9 years, both genders, 104 with normal weight(NW), 97 with Overweight-Obesity(OO Group) were included. Once the informed consent was signed we obtained the BMI, waist circumference, blood pressure(BP) and 5 mL of blood collected for glucose, cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, uric acid and insulin. As main outcome measures TyG or TG/HDL, HOMA-IR, and Receiving Operating Curves(ROC), sensitivity, specificity by ROC were obtained.
Results: Cutoff point TyG: 8.5 by ROC had an area under curve (AUC):0.802 IC95% 0.77to0.893, P = 0.0001; diagnostic accuracy of 73%. TG/HDL: 2.22; AUC:0.729 IC95% 0.622to0.837, P = 0.014; diagnostic accuracy of 52%. TyG can identify cardiometabolic alterations more than HOMA and TG/HDL. Cardiometabolic alterations in the OO group were hypertriglyceridemia:49.5%, low HDL:63.9%, IR:39.2% and in NW group were hypertriglyceridemia:30.8%, low HDL:60.6%, IR:9.6%.
Conclusions: We reported high frequency of hypertriglyceridemia and low HDL in Mexican children. TyG and TG/HDL are good predictors for IR. TyG has a better diagnostic accuracy. We need implementing TyG for identifying alterations and intervening in a timely manner to delay the onset of chronic diseases in children.

1. Introduction

Childhood obesity is a major public health problem in Mexico, according to the National Health and Nutrition Survey report in 2016, the combined prevalence of overweight and obesity in children was 32%, which represents more than 4.1 million of schoolchildren [1].

Given the current epidemic of childhood obesity, insulin resistance (IR) in children is also an important issue confronting health care professionals [2]. Even though there are still no clear criteria for defining IR in children, HOMA is the most widely used surrogate measure [3]. IR is related with metabolic abnormalities that favor the development of atherosclerosis, which in turn leads to cardiovascular events in later stages of life. To evaluate the cardiometabolic risk factors in schoolchildren [4] (glucose, dyslipidemia, waist circumference, IR, prehypertension) are necessary for preventing chronic disease in adulthood like diabetes, hypertension and cardiovascular disease, since in Mexico, the frequency of mortality in adults for cardiovascular disease (CVD) was 58% for men and 42% for women [5]. Presence of lesions without apparent

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clinical symptoms have been reported in younger ages due to overfeeding and poor exercising habits in childhood.

In adults, both Triglycerides/Glucose (TyG) and Triglycerides/HDL (TG/HDL) have been reported both as good predictors for IR. To our knowledge, there are few studies [6–10] that proven these indices in children. In Mexico, in a primary level attention (Family Medicine Units of Mexican Institute of Social Security, IMSS), insulin quantification is not a routine test, especially in the pediatric population; therefore the use of triage tests for diagnosis of IR in children is needed for identified clearly children with metabolic abnormalities. TyG and TG/HDL could be good indirect tests with less cost, for using in children in a primary level attention and we can initiate some non-pharmacologic or pharmacologic strategy. Our general objective was to evaluate the sensitivity and specificity of TyG and TG/HDL for predicting IR. We also compared the ability of TyG and TG/HDL to achieve an absolute diagnostic test sensitivity of >95%. In addition, we analyzed the magnitude of each cardiometabolic risk factor with TyG and TG/HDL in comparison with HOMA in children of 5–9 years with overweight – obesity and normal weight.

2. Methods

We realized a prospective, comparative cross-sectional study in 201 children between 5 and 9 years old; According to the percentile tables of the CDC corresponding to BMI and age, two groups were constituted: group with obesity-overweight (OO Group): ≥85th percentile (n = 97) and group with normal weight (NW Group): <percentile 85 (n = 104). Children with diabetes, hypertension, hypothyroidism or chronic illnesses, were exclusion criteria. A sample size was calculated [11]. We estimate a prevalence of IR of 30% [12] and a point of expected sensitivity of 95% and a minimal acceptable lower confidence limit of 88%. We planned to recruit 201 children. All children included were evaluated by the second author (M.V.U.T.) prior to study entry. This was a convenience sample of children when the second author was present in the Family Medicine Unit.

The study was conducted in Family Medicine Unit (FMU) No. 80 of IMSS of Morelia, Michoacán, Mexico and parents of the children who met the selection criteria were invited to participate in the study.

This study was approved by the Local Committee of Research and Ethics of Health Research of Social Security of Mexican Institute N° 1603 with number R-2015-1603-39 and it have been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. All parents were asked for their informed consent and the sign by agreement (assent) of the child for their participation in the study. Children who decided to withdraw from the study before the blood collection and children whose parents did not give their consent to obtain the blood sample, were excluded.

This study follows the Standards for Reporting Diagnostic Accuracy Studies (STARD).

Family and neonatal records were registered from their clinical records. Children Blood Pressure (BP) was measured with a standard clinical sphygmomanometer, using a stethoscope placed over the brachial artery pulse, proximal and medial to the cubital fossa, and 2 cm below the cubital fossa. Blood Pressure Cuff Bladder had a width of 9 cm, length 18 cm and a maximum arm circumference of 22 cm. We used the BP levels for boys by age and height percentile of Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents [13]. BP below 90th percentile was considered normal, BP between the 90th and 95th percentile as prehypertension and >95th percentile as hypertension. The measurements of the waist circumference (WC) were taken at the umbilical level. They were divided into percentiles for males and females; central obesity was defined when WC ≥ 90 percentile.

Body weight (Kg) was obtained on a scale with stadiometer with a clinical coat and without shoes, the measurement of height (m) in an upright position, with heels together and the feet separated at an angle of 60°, with the head in a horizontal plane of Frankfurt, free arms to the sides and the palms towards the hips. The heights and weights were assessed with a stadiometer using a fixed scale. The increments of the weight and height measurements were 0.1 kg and 0.01 m respectively. Body mass index (BMI) was calculated with the Quetelet equation (weight/height^2). The values obtained were classified by the percentile curves of CDC (*Centers for Disease Control and Prevention*)/NCHS (National Center for the Health Statistics [14].

A 7 mL blood sample was collected to determine levels of serum glucose, cholesterol, high, low and very low-density lipoproteins, triglycerides and uric acid, after a 12-h fasting. These determinations were made in the clinical laboratory of the FMU N° 80 IMSS. The analyses were performed using Vitros® 350 Chemistry System Ortho Clinical Diagnostics (NJ, USA). Low density proteins (LDL) were calculated using Friedewald equation. The other values of cardiometabolic risk factors were classified according to the Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents [13] which establishes the cut-off value for normal fasting glucose ≤100 mg/dL; high total cholesterol (TC) ≥200 mg/dL; high LDL ≥130 mg/dL; high triglycerides (TG) ≥100 mg/dL (0–9 years) and HDL value ≤ 45 mg/dL was considered low. Insulin was quantified by Insulin human Elisa Kit Invitrogen® with a sensibility of 0.17 μUI/mL and assay range of 5.1–250 μU/mL, our intraassay CV was 2.8%. We processed all serum sample by insulin in a one time by duplicated. In every child was evaluated IR with HOMA-IR = [Fasting glucose (mmol/L) x fasting insulin (μU/mL)]/22.5 and the cut point used was 8.23 that corresponding to ≥90th percentile. TyG was calculated as Ln[fasting triglycerides in mg/dL x fasting glucose in mg/dL]/2 [9]. TG/HDL [10] was calculated with fasting triglycerides/fasting HDL. The cutoff point of TyG [TyG = Ln(99.9 x 99.9/2)] = 8.5 and TG/HDL [TG/HDL = 99.9/44.9 = 2.22] Indexes were calculated using the normal parameters of Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents [13].

The numerical data were expressed as mean ± standard deviation and the categorical data were expressed as frequencies (%). The Kolmogorov-Smirnov normality test was performed to determine if the data were distributed normally or not. For the comparison of clinical variables between the group with and without obesity, the t Student test or U of Mann Whitney test were used. For the comparison between categorical variables, the X^2 test was used. Receiving Operating Curves (ROC) was realized for estimating the sensibility and 1-sensitivity of the cutoff point of TyG and TG/HDL. An odds ratio analysis (OR) was performed to evaluate the magnitude of each cardiometabolic risk factor with TyG and TG/HDL in comparison with HOMA in children. All tests were two sided, testing the hypothesis that TyG have better sensitivity that TG/HDL for predicting IR. The data was analyzed in the statistical package SPSS version 23. Differences were regarded as significant if p-value < 0.05.

3. Results

Between 1 March 2016 to 28 February 2017, 252 children were selected. The STARD diagram of children through study was reported in Fig. 1. Children were excluded (n = 51) because no accepted blood collection (n = 45) and we excluded six serum

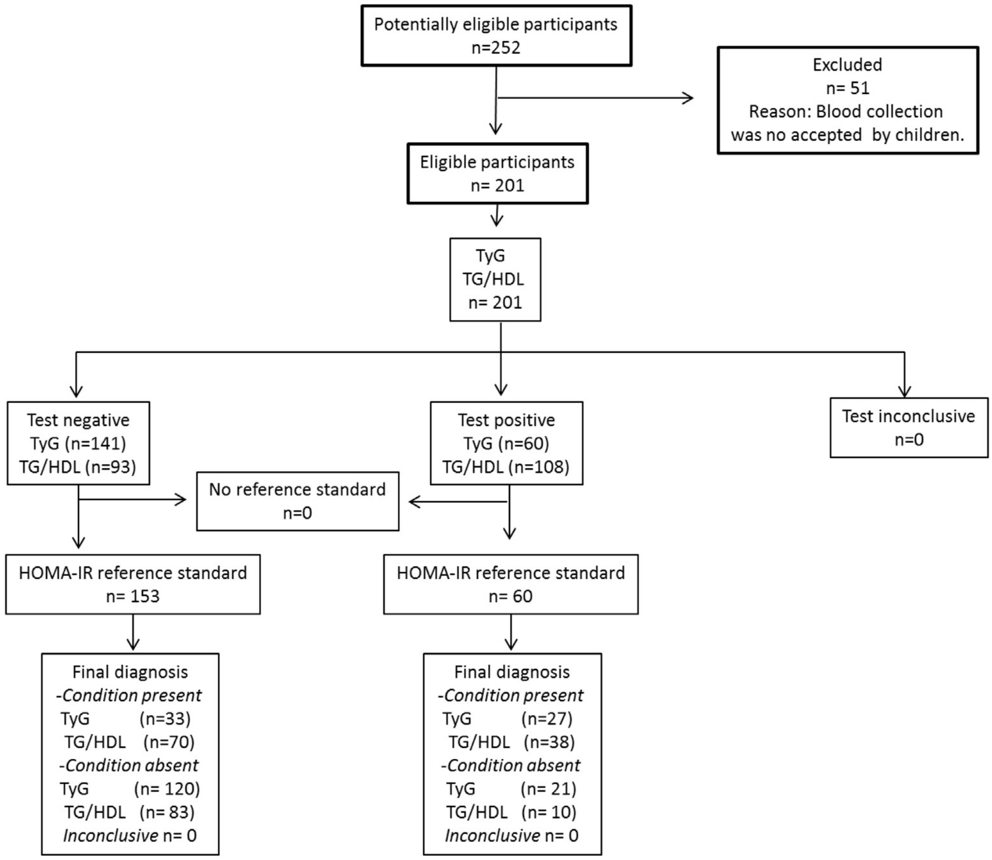

Fig. 1. The STARD diagram abstract.

samples by hemolysis. In total, 201 children completed the study. The median age of children was 8 years (range 5–9), and 42.78% were male. The median SBP was 90 mmHg (range 60–150) and DBP was 59 mmHg (range 40–99). Blood glucose levels were maintained in similar ranges. The median of HOMA-IR was 1.51 (range 0.21–38.45), median of TyG: 8.32 (range 7.20–9.92) and median of TG/HDL 2.17 (range 0.43–12.29). We compare these indexes between Obese-Overweight group (OO Group) and Normal Weight Group (NW Group) were statistically significant ($P < 0.05$).

Table 1 describes the cardiometabolic abnormalities in NW and OO children. We observed that only 31 of the children studied did not present any alteration in some biochemical variable, (OO Group: 11, NW Group: 20).

Table 1
Frequencies of cardiometabolic abnormalities of Overweight-Obese children and Normal Weight.

	OO Group n = 97 n (%)	NW Group n = 104 n (%)	P*
Prediabetes	13 (13.4%)	9 (8.7%)	0.281
Prehypertension	21 (21.6%)	14 (13.5%)	0.126
Hypercholesterolemia	29 (29.9%)	16 (15.4%)	0.014
Hypertriglyceridemia	48 (49.5%)	32 (30.8%)	0.007
HDL low	62 (63.9%)	63 (60.6%)	0.626
LDL high	23 (23.7%)	14 (13.5%)	0.061
Insulin Resistance	38 (39.2%)	10 (9.6%)	0.0001
Hyperuricemia	2 (2.06%)	2 (1.92%)	0.944
Low weight birth	4 (4.3%)	13 (12.9%)	0.033
High TyG ≥ 8.5	37 (38.1%)	23 (22.1%)	0.013
High TG/HDL ≥ 2.22	59 (60.8%)	49 (47.1%)	0.093

NW: Normal weight; OO: Overweight-Obese weight; HDL: High density lipoprotein; LDL: Low density lipoprotein; TyG: Triglycerides/Glucose Index; TG/HDL: Triglycerides/HDL Index. *X [2] Test; $p < 0.05$.

Receiver Operating Curves (ROC) was performed and the sensitivity, specificity and of the cut-off point of the established TyG and TG/HDL were recorded in Table 2 and Fig. 2.

Table 3 shows distribution of TyG and TG/HDL indexes for diagnosis of insulin resistance by HOMA in children.

Positive Predictive Value (PPV) of TyG = 8.5: 21.66%; Negative predictive Value (NPV) TyG = 8.5: 4.96%; accuracy diagnostic TyG = 8.5: 73.13%. PPV TyG = 8.38: 13.66%; NPV TyG = 8.38: 1.61%; accuracy diagnostic TyG = 8.38: 61.19%.

PPV TG/HDL = 2.22: 16.66% and NPV TG/THDL = 2.22: 2.15%; accuracy diagnostic TG/HDL = 2.22: 54.22%; PPV TG/HDL = 1.71: 13.66% and NPV TG/THDL = 1.71: 1.61%, accuracy diagnostic TG/HDL = 1.71: 39.80%.

To evaluate the magnitude of each cardiometabolic risk factor with TyG and TG/HDL in comparison with HOMA was realized Odds Ratio and the results were represented in Fig. 3. We analyzed ROC by each group (OO and NW) but no had any change in sensitivity and specificity values.

No significant adverse events occurred while blood sample collected. Only two children had a mild hematoma that disappeared in three days.

4. Discussion

The present study shows that either TyG or TG/HDL can be considerate as triage predictors for IR in schoolchildren of 5–9 years regardless of weight. Children with TyG ≥8.38 had two times more risk for having low HDL, and TG/HDL ≥1.71 three times more risk for high LDL, both important risk factors for cardiometabolic

Table 2
Cut-off points by ROC of the indices that predict insulin resistance in children.

Variable	Cut-off point	Sensitivity %	1-Specificity %	Area	Asymptotic significance	CI95%
TyG	8.5	65.0	25.7	0.802	0.0001	0.711–0.893
Proposed TyG	8.38	95.0	42.3			
TG/HDL	2.22	90.0	51.4	0.729	0.001	0.622–0.837
Proposed TG/HDL	1.71	95.0	68.6			

TyG: Triglycerides/Glucose Index; TG/HDL: Triglycerides/HDL Index.

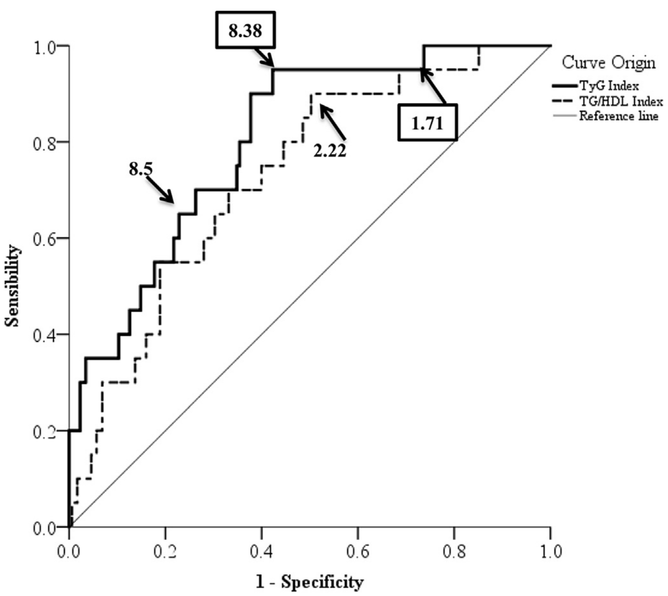

Fig. 2. Receiving Operating Curves of TyG and TG/HDL Index for predicting Insulin Resistance.

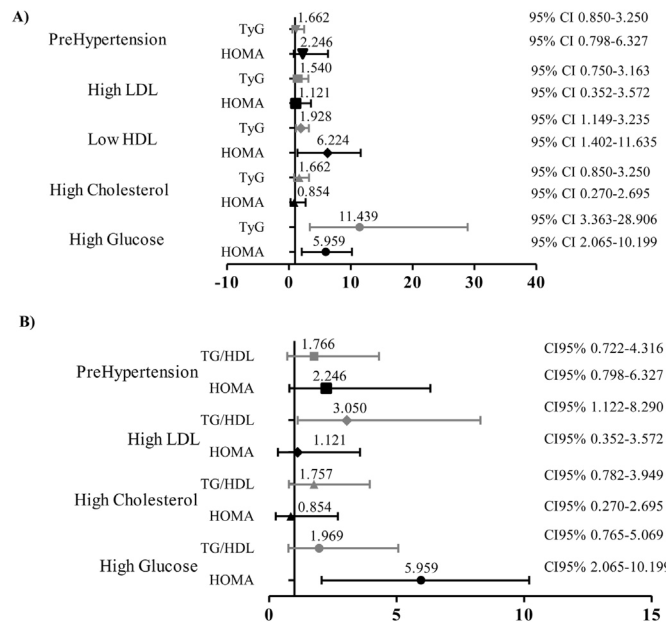

Fig. 3. Magnitude of cardiometabolic risks. A) TyG vs HOMA. B) TG/HDL vs HOMA.

Table 3
Contingency table of accuracy of TyG and TG/HDL for diagnosis of insulin resistance by HOMA in children.

HOMA-IR	Positive	Negative	Total
TyG = 8.5 Positive	13	47	60
Negative	7	134	141
Total	20	181	201
TyG = 8.38 Positive	19	77	139
Negative	1	104	62
Total	20	181	201
TG/HDL = 2.22 Positive	18	90	108
Negative	2	91	93
Total	20	181	201
TG/HDL = 1.71 Positive	19	120	139
Negative	1	61	62
Total	20	181	201

disease.

This study had limitations. First, blood collection was not accepted in all children, curiously the children with more age and with more obesity did not accept the collection of the blood, probably because of overprotection of parents to children with obesity so frequent in our environment. Second, we had 6 serum sample with hemolysis that may cause some interference during sample processing. We tried to control all possible bias. *Selection bias*, the sample included in the study is representative of the FMU Nº 80 population and we choose first an obese child and was paired with another of the same sex and age, ought to exclusions we completed 201 children (sample size calculated: 169 children). *Verification bias*, the reference test was applied to all study subjects, and diagnostic confirmation of all study subjects was obtained, and all diagnostic tests had applied and interpreted blindly and independently to avoid the *bias of Diagnostic Suspicion*.

In Mexico, one of the problems that have been observed with the increase in the prevalence of obesity in children is the increase in a myriad of complications related to their presence, among which included metabolic, orthopedic and psychological complications are. In this study, we observed that there is a statistically significant difference in systolic/diastolic blood pressure ($P < 0.05$) and a high frequency of prehypertension based on routinely collected clinical data in the OO (21.6%) and NW group (13.5%) ($p = 0.126$). Koebnick et al. [15] realized a population-based cross-sectional study in 237,248 pediatric population and obtained a prevalence of 29.6% in Hispanic children of 6–11 years old. This prevalence is lower to that reported in this study (35.1%, in both groups), however, the number of children evaluated by Koebnick is a thousand times greater. These results are worrisome since it confers a high risk to develop chronic diseases (diabetes, metabolic syndrome, hypertension, cardiovascular disease) in children of

Morelia, Michoacán, Mexico.

In North of Mexico, Rodríguez-Moran et al. [16] identified hyperglycemia (0.3%), hypertension (3.4%), hyperinsulinemia (13.4%) and elevated waist circumference in 29.3% of 358 children of 6–10 years, frequencies different from those reported in this study and proves that ethnic and racial origin, genetic factors, dietary habits and lifestyle seem to be determining factors in development of metabolic alterations in children. The increased caloric intake rather than the dietary macronutrient composition is associated with IR and hyperinsulinemia. Limited cross-sectional data suggest that dietary saturated fat and sugar-sweetened beverages may be associated with alterations in insulin sensitivity and secretion [17]. One limitation of this study was that the food and beverages intake of the children enrolled in this study were not recorded.

Abnormalities in the cardiometabolic parameters are associated with childhood obesity and it has also been observed in other studies [18], with strong determinants of the lipid profile and insulin. It is well known that dyslipidemia is one of the frequently associated characteristics in children with metabolic syndrome. The high prevalence of low HDL cholesterol and triglyceride showed in this study are alterations frequently described in México [16] ought to high carbohydrate intake and sedentary lifestyle of children. In addition, the decrease in HDL affects the reverse transport of cholesterol, which is the metabolic pathway responsible for the removal of cholesterol from the peripheral cells and its transport to the liver for recycling or elimination [17]. Is well understood that triglycerides-rich lipoproteins can stimulate the recruitment of monocytes in the vascular wall, since they increase the expression of monocyte chemoattractant protein (MCP)-1 by endothelial and smooth muscle cells, the expression of endothelial adhesion molecules (VCAM-1, ICAM-1) with the consequent adhesion of monocytes to the endothelium [19] and a mitochondrial dysfunction is presented [20]. These changes occur in cardiac muscle and can be often detected before the onset of hyperglycemia, although there is controversy if these are primary or secondary changes ought to obesity [21,22] and could potentially contribute to changes in cardiac metabolism of obese children.

There is no international consensus regarding the use of the cutoff point of HOMA-IR in children. Peplies J et al. [23] in their study IDEFICS in preadolescents children report that a value of HOMA-IR $\geq$90th percentile can be considerate for monitoring purposes and HOMA-IR $\geq$95th percentile to define for clinical action.

TyG and TG/HDL have been reported as surrogate markers for the assessment of IR in adults and children [6,24] and they could be a useful marker in the identification of cardiovascular risk factor. TyG has been positively associated with unhealthy dietary pattern. Vieyra Ribeiro et al. [7] in Brazilian children reported a TyG cutoff point to predict IR of 7.88 with a sensitivity of 80% and specificity of 53.2% and a prevalence of IR of 42.3%. In this study in Mexican children with cutoff point of HOMA $\geq$90th percentile (value: 8.23), we identified a 9.95% of children with IR. With cutoff point TyG of 8.38 we obtained a sensitivity = 95% and specificity = 42.3%, an area under receiving operating curve (AUROC) = 0.802 and diagnostic accuracy of 61.19%. With TyG$\geq$7.88 proposed by Vieyra [7] could have positive false data in our population ought to low diagnostic accuracy that it was of 26.86%.

TG/HDL has been reported as a good predictor of IR in adults. The cutoff point of 2.22 in children, we obtained a sensitivity = 90% and specificity = 51.4%, AUROC = 0.729 and a diagnostic accuracy of 52.82%. The magnitude of OR by TyG is almost two times more probable for identifying a low HDL that is considered a cardiometabolic abnormality, while TG/HDL only can predict a high LDL.

The possibility of obese children to become obese adults, sedentary and with metabolic changes is higher. The cardiometabolic risk factors present in this population show the needing of implementing programs that allow identifying them and intervening in a timely manner to reduce their impact on the quality life in children. Is necessary to define clinical and laboratory indicators for diagnosis of IR in overweight or obese children. The utilization of both indexes should be implemented as a triage prognostic for making actions that could change the course of cardiovascular disease.

We concluded that this study provides evidence of both TyG and TG/HDL in Mexican children could be as triage predictors for IR. TyG has a better diagnostic accuracy than TG/HDL. We reported a high frequency of hypertriglyceridemia and low HDL in obese children.

Contributors

MVUT, DCVS and AGG are responsible for drafting of manuscript. CAA and AGG are responsible for critical revision of manuscript.

Conflicts of interest

None declared.

Data sharing statement

No additional data are available.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2019.05.020.

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