Triglycerides/high-density lipoprotein-cholesterol ratio in children with metabolic syndrome

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ABSTRACT
The incidence of metabolic syndrome in children is increasing due to the obesity epidemic. Accessible biochemical studies are required to diagnose and treat it in a timely manner. This cross-sectional study aims to assess the usefulness of the triglycerides/high-density lipoprotein-cholesterol (TG/HDL-c) index as a predictor of metabolic syndrome according to the diagnostic criteria of the European initiative Identification and prevention of Dietary- and lifestyle-induced health Effects In Children and infantS (IDEFICS) in obese children 3 to 10 years of age. Descriptive, observational, retrospective study in the pediatric service of León General Hospital, Guanajuato, México, from January 2017 to December 2018. In a group of 73 obese children aged 3 to 10 years, it was found that the TG/HDL-c ratio has an odds ratio of 6 (95% CI 2–18) as a predictor of metabolic syndrome. A cut-off point of 2.4 for this index has a sensitivity of 85%, specificity of 85%, likelihood ratio of 5.6, positive predictive value of 94%, and negative predictive value of 68% to diagnose metabolic syndrome with IDEFICS criteria. The TG/HDL-c index is a useful indicator to diagnose metabolic syndrome in children 3 to 10 years of age with obesity, in whom it is not possible to perform a comprehensive biochemical study.

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KEYWORDS Triglycerides/HDL-cholesterol ratio; metabolic syndrome; children

Introduction

Obesity in pediatric age has become a worldwide epidemic, which has led to the observation of cardio-metabolic complications from early stages of life and during adulthood (Cornejo-Barrera and Llanas-Rodríguez 2013). It is estimated that 80% of overweight children will be obese adults (Burguete-Garcia et al. 2014). Obesity corresponds to 6.3% of all disability-adjusted life years (DALYs) at all ages, including pediatric age (GBD 2015).

The study of the European initiative called Identification and prevention of Dietary- and lifestyle-induced health Effects In Children and infantS (IDEFICS) is a cohort study of 16,228 children between 2 and 10 years of age in a population
of 8 countries (Sweden, Germany, Hungary, Italy, Cyprus, Spain, Belgium and Estonia) with which they built percentiles for the metabolic syndrome criteria and considered the 90th percentile level for waist circumference, blood pressure, triglycerides, glucose and homeostatic model assessment of insulin resistance (HOMA-IR), as well as the 10th percentile for high-density lipoproteins-cholesterol (HDL) as the cut-off point for diagnosing metabolic syndrome at the monitoring level. The 5th percentile for HDL and the 95th percentile for the rest of the parameters was the cut-off point for considering metabolic syndrome at the intervention level (Ahrens et al., 2014) (Table 1).

These authors compared the frequency of metabolic syndrome with the definitions already established by Cook et al., Viner et al. and the definition of the International Diabetes Federation (IDF). The definition suggested by the IDEFICS initiative had the highest prevalence (5.5%), while that of the IDF group resulted in the lowest prevalence (0.4%). The definition of Cook et al. obtained a 1.4% prevalence and that of Viner et al. 0.9%. Except for the IDF definition, the prevalence was higher in girls than in boys (Ahrens et al., 2014). More recent publications with meta-analyses that include populations from several countries, including Mexico, coincide in showing that the IDF criteria underestimate the frequency of metabolic syndrome in children (Rodríguez-Morán et al. 2004; Bitew et al. 2020; Reisinger et al. 2021), especially in those under 10 years of age, which supports the use of criteria based on percentiles as proposed by the IDEFICS initiative.

In developing countries, it is difficult to measure all biochemical parameters to meet the diagnostic criteria for metabolic syndrome. This is why several authors have suggested the use of indices using serum lipids to surrogates the measurement of insulin and identify cases of insulin resistance before the rise in blood glucose levels, and thus early identify cases of metabolic syndrome. In both children and adults, it has been proposed that the triglyceride to high-density lipoprotein ratio (TG/HDL-c) is a marker to identify subjects with cardiometabolic risk (Li et. 2018; Nur Zati Iwani et al. 2019; Vallée et al. 2019).

It has even been considered that the measurement of this index in pregnant women with gestational diabetes may be useful to predict macrosomia in the product (Liu et al. 2020).

Krawczyk M et al. compared TG/HDL-c values in eutrophic and obese children with a mean age of 11 years, finding values of 1.3 (interquartile range – IQR- 0.9–4.3) vs 2.9 (IQR 0.5–14.3) respectively. When comparing children with and without metabolic syndrome, the difference was 2.74 (IQR 0.55–12.72) vs 5.33 (IQR 2.53–14.31) respectively. They calculated that for each unit of increase in TG/HDL-c, the odds ratio for having metabolic syndrome was 2.09 (95% CI: 1.37–3.2) (Krawczyk et al. 2018).

In Egypt, Behiry EG et al. compared the usefulness of the TG/HDL-c index instead of the HOMA index as a marker of insulin resistance in
Table 1. Cut-off points by age and sex of the two proposed definitions of metabolic syndrome with the 90th percentile corresponding to the level of monitoring and the 95th percentile corresponding to the level of intervention (IDEFICS).

|                      | EXCESS OF ADIPOSITY | BLOOD PRESSURE | LIPIDS IN BLOOD | GLUCOSE METABOLISM |
|----------------------|---------------------|----------------|-----------------|-------------------|
|                      | WC (cm) P90 | WC (cm) P95 | SBP (mmHg) P90 | SBP (mmHg) P95 | DBP (mmHg) P90 | DBP (mmHg) P95 | Trg (mg/dL) P90 | Trg (mg/dL) P95 | HDL (mg/dL) P05 | HDL (mg/dL) P09 | Glu (mg/dL) P90 | Glu (mg/dL) P99 |
| BOYS age in years    |         |         |               |               |                |                |                |                |                |                |                |                |
| 3–3.9                | 52.7     | 53.8    | 105.4         | 108.8         | 69             | 71.6           | 84.6           | 107           | 31.3          | 26.8           | 1.03           | 1.35           | 92.2           | 95.9           |
| 4–4.9                | 54.5     | 55.6    | 107.5         | 111           | 69.7           | 72.4           | 84.6           | 107           | 33.3          | 28.7           | 1.26           | 1.62           | 93.6           | 97.3           |
| 5–5.9                | 56.2     | 57.5    | 109.6         | 113.1         | 70.4           | 73.1           | 84.6           | 107           | 35.3          | 30.6           | 1.42           | 1.8            | 94.9           | 98.7           |
| 6–6.9                | 58       | 59.5    | 111.3         | 115           | 71             | 73.7           | 84.6           | 107           | 37.2          | 32.3           | 1.55           | 1.94           | 96.3           | 100            |
| 7–7.9                | 59.8     | 61.5    | 113.1         | 116.8         | 71.5           | 4.3            | 84.6           | 107           | 38.5          | 33.6           | 1.66           | 2.06           | 97.7           | 101.4          |
| 8–8.9                | 61.7     | 63.6    | 114.9         | 118.6         | 72.1           | 34.9           | 84.6           | 107           | 39.2          | 34.3           | 1.85           | 2.26           | 99.1           | 102.8          |
| 9–9.9                | 63.7     | 65.8    | 116.3         | 120.1         | 72.6           | 37.5           | 84.6           | 107           | 39.7          | 34.9           | 2.14           | 2.58           | 100.4          | 104.1          |
| 10–10.9              | 65.7     | 68.3    | 117.8         | 121.6         | 73.2           | 76             | 84.6           | 107           | 40.4          | 35.6           | 2.43           | 2.9            | 101.8          | 105.5          |
| GIRLS age in years   |         |         |               |               |                |                |                |                |                |                |                |                |
| 3–3.9                | 52.5     | 53.8    | 106           | 109.8         | 70.2           | 72.8           | 93.1           | 115.9         | 29.3          | 24.9           | 1.21           | 1.55           | 89.8           | 93.3           |
| 4–4.9                | 54.3     | 55.6    | 107.9         | 111.6         | 70.7           | 73.4           | 93.1           | 115.9         | 31.5          | 27             | 1.34           | 1.7            | 91.1           | 94.6           |
| 5–5.9                | 55.8     | 57.3    | 109.7         | 113.4         | 71.3           | 74             | 93.1           | 115.9         | 33.5          | 28.8           | 1.47           | 1.84           | 92.4           | 95.9           |
| 6–6.9                | 57.4     | 58.9    | 111.2         | 114.8         | 71.8           | 74.4           | 93.1           | 115.9         | 35.5          | 30.7           | 1.55           | 1.91           | 93.7           | 97.2           |
| 7–7.9                | 59.2     | 60.9    | 112.7         | 116.3         | 72.2           | 74.9           | 93.1           | 115.9         | 37            | 32.1           | 1.69           | 2.06           | 95             | 98.5           |
| 8–8.9                | 61.3     | 63.2    | 114.2         | 117.7         | 72.7           | 75.4           | 93.1           | 115.9         | 37.9          | 33             | 1.96           | 2.36           | 96.3           | 99.8           |
| 9–9.9                | 63.8     | 65.9    | 115.7         | 119.2         | 73.1           | 75.9           | 93.1           | 115.9         | 38.2          | 33.4           | 2.35           | 2.79           | 97.6           | 101.1          |
| 10–10.9              | 66.6     | 68.9    | 117.3         | 120.7         | 73.6           | 76.3           | 93.1           | 115.9         | 38.3          | 33.6           | 2.78           | 3.27           | 98.9           | 102.4          |

WC—waist circumference, SBP—systolic blood pressure, DBP—diastolic blood pressure, Trg—serum triglycerides, HDL—high-density lipoproteins, HOMA—homeostatic model assessment, Glu—serum glucose

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overweight and obese children, finding that a cut-off point of >1.36 had a sensitivity of 85.7% and specificity of 66.7% for diagnosing insulin resistance in children older than 5 years (Behiry et al. 2019).

Acosta-García E et al. in Venezuela calculated quartiles for the values of the TG/HDL-c index and related it to the waist-height index to propose a cardio-metabolic index as a predictor of cardiovascular risk factors in adolescents. They established a value of 2.25 as the level of the third quartile (Acosta-García and Concepción-Páez 2018).

Azizí-Soleiman F et al. calculated reference values for serum lipids in children aged 7 to 18 years in Iran, finding that TG/HDL-c values are higher in males in older age groups, but in the female sex, this increase is only found in groups with levels above the 50 percentile (Azizí-Soleiman et al. 2020).

Özalp Kızilay D et al. in Turkey studied 128 children aged 8 to 18 years and used the cut-off point of 2.2 for the triglycerides/HDL cholesterol index (TG/HDL-c) as a cardiovascular risk factor (Özalp Kızilay et al. 2019).

Rumińska M et al. studied children aged 10 to 17 years in a hospital weight control program in Poland and found that children who gained weight had a higher TG/HDL-c ratio than those who decreased or maintained their weight without changes (Rumińska et al. 2019).

This cross-sectional study aims to assess the usefulness of the triglycerides/high-density lipoprotein-cholesterol (TG/HDL-c) index as a predictor of metabolic syndrome according to the diagnostic criteria of the European initiative Identification and prevention of Dietary- and lifestyle-induced health EFects In Children and infantS (IDEFICS) in obese children 3 to 10 years of age seen in the outpatient clinic of the pediatric service of the León General Hospital from January 2017 to December 2018.

**Methods**

**Study design**

A retrospective cross-sectional survey was carried out.

Patients of both sexes were included, aged from 3 years to 10 years, with a body mass index (BMI) (weight [kg]/height [m])Burguete-García et al. 2014) greater than or equal to the 95th percentile according to the graphs of the Centers for Disease Control and Prevention (CDC) version 2000 (U.S. Department of Health & Human Services 2017). Those with congenital malformations and those under steroid treatment were excluded.

To calculate the sample size, the publication of Ahrens W et al. (Ahrens et al., 2014) was considered, who reported a frequency of metabolic syndrome of 5.5%, a precision of 5%, a confidence level of 95% and a power of 80% were used; thus, a total of 73 patients were obtained.
**Data collection**

The variables measured were age, sex, weight, height, BMI, waist circumference, blood pressure, and serum levels of triglycerides, HDL cholesterol, glucose, and fasting insulin. The HOMA-IR index was calculated with the formula \([\text{glucose (mg/dL)} \times \text{insulin (microUnits/mL)}/405]\). ISAK methodology was used for somatometry with a single evaluator. Blood pressure measurement was performed with an aneroid baumanometer using braclets according to the arm length of each patient. Glucose, triglycerides and HDL cholesterol measurements were made with the automated spectrophotometry technique and serum insulin was measured with the electrochemiluminescence technique in the laboratory of León General Hospital. A diagnosis of metabolic syndrome was made with three or more criteria according to IDEFICS: 90th percentile cut-off point for all parameters, except HDL cholesterol, at the 10th percentile (Table 1). For the group of 10-year-old children, a second analysis was made using criteria from the International Diabetes Federation (IDF) 7 and the waist circumference percentiles for Mexican children published by Fernández JR et al. (Fernández et al. 2004).

**Statistical analysis**

Descriptive statistics with mean and standard deviation were used for continuous numerical variables with normal distribution and with median and interquartile range for numerical variables that did not have normal distribution. The kurtosis test was applied to determine normality in the distribution. Percentages were used for nominal variables. Chi-square and Student’s t or Mann–Whitney U were used to compare the groups with and without syndrome. A multivariate analysis was performed with step-by-step backward logistic regression. A value of \(p < 0.005\) was considered to be significant. The power for the difference of numerical variables was calculated, considering a level greater than 80% adequate. Diagnostic tests were analyzed for the TG-HDL-c index and the diagnosis of metabolic syndrome, calculating sensitivity, specificity, negative predictive value, negative predictive value and likelihood ratio. ROC curve was constructed in an empirical model. Statistical package NCSS 2004 was used.

**Results**

Seventy-three records of Mexican children with obesity were reviewed, of whom 36 were boys and 37 girls, with a median age of 8 years (IQR- 7-10).

All patients had central adiposity according to the waist circumference measurement (greater than the 95th percentile).
Table 2. Clinical and laboratory characteristics comparing the groups with and without metabolic syndrome.

| VARIABLE                  | Obesity without metabolic syndrome (n = 20) | Obesity with metabolic syndrome (n = 53) | p value | Power |
|---------------------------|--------------------------------------------|----------------------------------------|---------|-------|
| AGE (years)               | 7 ± 2.3                                    | 8.2 ± 1.8                              | 0.007   | 79%   |
| SEX (Female/Male)         | 8/12                                       | 29/24                                  | 0.02    |       |
| WEIGHT (kg)               | 35.5 ± 9.5                                 | 45.9 ± 12.5                            | <0.001  | 96%   |
| HEIGHT (cm)               | 125 ± 14                                   | 136 ± 13                               | 0.001   | 92%   |
| BMI (kg/m²)               | 22.2 ± 2.5                                 | 23.3 ± 3.4                             | 0.007   | 79%   |
| WAIST (cm)                | 71.4 ± 8                                   | 80.9 ± 9.5                             | <0.001  | 99%   |
| SYSTOLIC PRESSURE (mmHg)  | 93 ± 13                                    | 99 ± 13                                | 0.04    | 54%   |
| DIASTOLIC PRESSURE (mmHg) | 53 ± 9                                     | 58 ± 11                                | 0.03    | 59%   |
| TRIGLYCERIDES (mg/dL)     | 79.5 (68–103.5)                             | 146 (104–183)                          | <0.001  | 99%   |
| HDL (mg/dL)               | 43.8 ± 11.6                                | 37.6 ± 9.4                             | 0.01    | 49%   |
| GLUCOSE (mg/dL)           | 84.4 ± 6.1                                 | 92.9 ± 37.8                            | 0.16    | 26%   |
| INSULIN (µU/ml)           | 7.3 (5.8–10)                               | 14.9 (12.4–23)                         | <0.001  | 96%   |
| HOMA-IR INDEX             | 1.5 (1.2–2.1)                              | 3.2 (2.6–5)                            | <0.001  | 93%   |
| TG/HDL-c INDEX            | 2 (1.6–2.3)                                | 3.8 (2.7–5.8)                          | <0.001  | 91%   |

*Mean, standard deviation, student’s t \( ^b \)Fisher’s exact test \( ^c \)Median, interquartile range, Mann–Whitney U

In eight cases (11%), no criteria for metabolic syndrome other than central adiposity were found. In 12 cases (16.4%), there was only one criterion of metabolic syndrome in addition to central adiposity.

In 53 cases (72.6%) 3 or more criteria for metabolic syndrome were met. Table 2 shows the clinical and laboratory characteristics of both groups.

The frequency of alteration of each parameter of the metabolic syndrome was: high HOMA index 55 cases (75%), hypertriglyceridemia 52 cases (71%), low HDL-c 32 cases (44%), systolic arterial hypertension 8 cases (11%), diastolic arterial hypertension 5 cases (7%).

In the multivariate analysis with logistic regression, all the variables that showed a significant difference in the univariate analysis were included and only the TG/HDL-c index remained measured as a continuous numerical variable (OR 6, 95% CI 2 – 18).

The ROC curve analysis of the empirical model (Figure 1) showed an area under the curve of 89% with a cut-off point of 2.4 for the TG/HDL-c index has a sensitivity of 85%, specificity of 85%, likelihood ratio of 5.6, positive predictive value of 94% and 68% negative predictive value for diagnosing metabolic syndrome with IDEFICS criteria.

A second analysis was performed for the group of patients who were 10 years or older (n = 20) using IDF criteria and the waist circumference percentiles for Mexican children, finding a frequency of metabolic syndrome of 45%. The TG/HDL-c index showed an OR 3 (95% CI 1.2–7.6, p = 0.02) as
a predictor of metabolic syndrome. Using the IDEFICS criteria only for this age group, a frequency of metabolic syndrome of 85% was found.

**Discussion**

The frequency of metabolic syndrome that we found in our study is higher than that previously reported in the population of children with obesity. Bitew et al. 5 conducted a meta-analysis in which they found a frequency of 56.32% using the Ferranti criteria. Our study found 72.6%, which can be explained because the study subjects are patients from a regional referral hospital who previously passed through primary care centers without achieving improvement.

Our study confirms the usefulness of the TG/HDL-c index as a diagnostic test to identify children under 10 years of age with metabolic syndrome. In developing countries, it is often not possible to carry out the complete biochemical study to integrate the diagnosis of metabolic syndrome, so it is useful to have tests that surrogate the others.

Previous studies reported usefulness of this index in a range of values from 1.4 to 2.9 (Krawczyk et al. 2018; Acosta-García and Concepción-Páez 2018; Behiry et al. 2019; Özalp Kızılay et al. 2019; Azizi-Soleiman et al. 2020) in obese children from different parts of the world. The cut-off point of 2.4 found in our study is closer to the point reported in the Latin American population by Acosta et al. (Acosta-García and Concepción-Páez 2018), which was 2.25, which suggests that genetics play an important role in the behavior of lipid metabolism from early stages of life.

The study of the metabolic conditions of children with obesity is a priority in clinical research since in many countries overweight and obesity is a public health problem.
health problem. In Mexico, an epidemiological alert has been issued since 2016 due to the rapid increase in deaths from chronic non-communicable diseases (Secretaría de Salud Subsecretaría de Prevención y Promoción de la Salud 2016, 2018). This has led to an intentional search for metabolic alterations in young children using instruments such as the IDEFICS tool (Bundesministerium für Gesundheit).

With the emergence of the SARS-CoV-2 virus pandemic, it became clear that obesity and its metabolic complications are an important risk factor for severe forms of COVID-19. Although this disease in children usually causes mild symptoms or is asymptomatic, it is in the pediatric age group that metabolic syndrome must be detected and treated early to prevent this condition from persisting into adulthood and resulting in a decrease in the quality and life expectancy.

Our results add to the evidence supporting the biochemical study of children with obesity, using diagnostic tools that are easily accessible even in low-income countries.

**Limitations**

One limitation of the study is that it only included obese children, so it is important to carry out studies that analyze the behavior of glucose metabolism disorders and the TG/HDL-c index in overweight children.

**Conclusion**

The TG/HDL-c index is a useful indicator to diagnose metabolic syndrome in children 3 to 10 years of age with obesity, in whom it is not possible to perform a comprehensive biochemical study.

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**Ethics approval**

To carry out this study, authorization was obtained from the research ethics committee of the León General Hospital with the registration number SSGTO0171.

**Disclosure statement**

All authors declare that they have no conflicts of interest.
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Authors’ contributions
RJMC designed the study, and LAM performed the data collection. Both authors were involved in the analysis and interpretation of data, and the revisión of the manuscript and approved the final submitted manuscript.

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