

Research article

Doi: 10.4274/jcrpe.galenos.2019.2019.0024

Triglyceride Glucose Index as a Surrogate Measure of Insulin Sensitivity in a Caucasian Pediatric Population

Running Head: Triglyceride Glucose Index in a Caucasian Children

¹Valeria Calcaterra, ¹Chiara Montalbano*, ²Annalisa de Silvestri*, ³Gloria Pelizzo, ¹Corrado Regalbuto, ¹Valeria Paganelli,

⁴Riccardo Albertini, ¹Francesco Delle Cave, ¹Daniela Larizza, ⁶Hellas Cena

¹Department of the Mother and Child Health, Pediatric Unit, Fondazione IRCCS Policlinico San Matteo and Department of Internal Medicine University of Pavia, Pavia, Italy

²Biometry & Clinical Epidemiology, Scientific Direction, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

³Pediatric Surgery Department, Children's Hospital "G. di Cristina", ARNAS "Civico-Di Cristina- Benfratelli", Palermo, Italy

⁴Laboratory of Clinical Chemistry, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

⁵Department of Public Health, Experimental and Forensic Medicine, Unit of Human Nutrition, University of Pavia Pavia, Italy

*Equal contribution

Abstract

Objective: The triglyceride and glucose (TyG) index has been proposed as a simple surrogate of insulin resistance (IR) with high sensitivity as an IR index besides the well known homeostasis model assessment of IR (HOMA-IR). Limited data are reported in children. We investigated the sensitivity and specificity of TyG index in a pediatric Caucasian population, as a surrogate measure of IR and compared the results with HOMA-IR.

Methods: We enrolled 541 children (11.7±2.71 yrs). According to body mass index (BMI) chart, the subjects were divided into three groups: normal weight BMI<75th percentile, overweight BMI 75th–95th percentile, and obese>95th percentile. TyG index was calculated as $(\ln[\text{fasting triglycerides}(\text{mg/dl}) \times \text{fasting plasma glucose}(\text{mg/dl})/2])$ and considered pathological when exceeding 7.88. HOMA-IR was calculated as $(\text{insulin} \times \text{glucose})/22.5$ and defined pathological whenever exceeding 97.5th percentile for age and sex.

Results: In children with overweight/obesity TyG index was higher compared to normal weight subjects ($p<0.001$). TyG index was correlated with BMI ($p<0.001$); WHtR ($p<0.001$), total and HDL cholesterol ($p<0.001$); ALT ($p<0.001$), blood pressure ($p<0.001$). A correlation between TyG index and HOMA-IR ($p<0.001$) as well as high TyG index and pathological HOMA-IR ($p<0.001$) were noted. The optimal cut-off for IR was considered 7.98 (sensitivity 60%; specificity 78%; AUC 0.69).

Conclusions: TyG index is a useful and cost-effective index of IR among children and adolescents. The cutoff 7.98 may be used for IR risk screening in childhood obesity, but we recommend caution when used in other populations.

Keywords: Triglyceride glucose index, insulin resistance, children, adolescents, HOMA-IR, obesity

What is already known on this topic?

- Children with obesity commonly exhibit insulin resistance, disturbances in lipoprotein metabolism, and increased serum triglyceride levels.
- The triglyceride and glucose (TyG) index has been proposed as a simple surrogate of insulin resistance (IR).
- Limited data are reported in children.

What this study adds?

- We detected a good sensitivity and specificity of the TyG index as a surrogate measure for predicting IR in children and adolescents with overweight/obesity.
- This index is correlated to abdominal obesity and dismetabolic profile.
- TyG index compared to HOMA-IR, is not influenced by pubertal stage.

Correspondence: Dott.ssa Valeria Calcaterra, Department of Maternal and Children's Health Pediatric Endocrinology Unit

Fondazione IRCCS Policlinico S. Matteo and University of Pavia P.le Golgi n.2, 27100 Pavia, Italy

Phone: +390382502930

e-mail: v.calcaterra@smatteo.pv.it

0000-0002-2137-5974

Submitted: 12-Feb-2019

Accept: 15-May-2019

Introduction

Children with obesity commonly exhibit insulin resistance, disturbances in lipoprotein metabolism, and increased serum triglyceride levels (1-2). Correlation between hypertriglyceridemia and insulin resistance (IR) remains not fully elucidated (3-7). It has been reported that triglycerides increase interferes with muscle-glucose metabolism (3) and may be correlated to insulin sensitivity decrease (4).

The homeostasis model assessment of insulin resistance (HOMA-IR) index is a validated and widely used index to evaluate insulin resistance using measures derived from the fasting state in epidemiological studies and has also been used in clinical practice (4-8). However, a plasma insulin assay is not yet available in all laboratories, has poor reproducibility and is expensive (9). Recently, in adults the triglyceride and glucose (TyG) index has been proposed as a simple surrogate of IR with high sensitivity in recognizing insulin resistance compared with the HOMA-IR (8-11) and euglycemic-hyperinsulinemic clamp (7). It is useful for insulin resistance detection in large-scale apparently healthy subjects or for the early identification of patients at risk of diabetes (12). TyG index is considered the best predictor of developing diabetes in normoglycemic (12) and pre-diabetic patients (13, 14).

Limited data are reported in pediatric age, in which the TyG index has been described as a useful predictor of metabolic abnormalities in Asian, Mexican American, Non-Hispanic White adolescents (15-21). Until now there is no consensus for reference criteria in Caucasian children, besides no pediatric study has been conducted on this topic.

The aim of the present study was to investigate the sensitivity and specificity of the TyG index in a pediatric Caucasian population, as a surrogate measure of IR in children and adolescents with overweight/obesity and to compare it with the established marker, HOMA-IR. An optimal cut-off of TyG index for IR was also identified.

Patients and Methods

Patients

We enrolled 541 Caucasian Italian children and adolescents aged 11.7 ± 2.71 years (266 females and 275 males) referred to our outpatients' clinic for auxological evaluation or obesity by their general practitioner or primary care pediatrician.

According to the Italian Society for Pediatric Endocrinology and Diabetology (ISPED) criteria (22), the subjects were divided into three groups:

- Subjects with obesity (group 1): BMI that exceeded the 95th percentile for the age and sex (23),
- Subjects with overweight (group 2): BMI 75th–95th percentile (23),
- Subjects with normal weight (group 3): BMI < 75th percentile (23).

Exclusion criteria were: specific intestinal symptoms and intestinal diseases, known secondary obesity conditions, use of any medications, and concomitant chronic or acute illnesses.

Ethics

This study was conducted according to the Good Clinical Practice guidelines and was approved by the Human Ethic Committees of Fondazione IRCCS Policlinico S. Matteo of Pavia (Protocol number: 20150005231). All participants or their responsible guardians gave their written consent after being informed about the nature of the study.

Physical examination

The physical examination of the participants included evaluation of height, weight, waist circumference, BMI, pubertal stage according to Marshall and Tanner (24-25), and blood pressure (BP) measurement.

Height, weight and waist circumference measurement, were performed as previously reported (26). Waist to height ratio (WHtR) was calculated according to Maffeis (27).

BMI was calculated as body weight (kilograms) divided by height (meters squared). Pubertal development was classified as: stage 1 = Tanner 1; stage 2 = Tanner 2–3; and stage 3 = Tanner 4–5.

Systolic (SBP) and diastolic (DBP) blood pressure were measured twice using a mercury sphygmomanometer, after the participant sat comfortably for 5 min, with an appropriately sized cuff on the right arm, which was slightly flexed at heart level (28). The second BP measurement was used for analysis. Elevated SBP or DBP was defined with values exceeding the 95th percentile for age and sex (29).

Biochemical parameters and definitions

Blood samples were drawn in the morning, after an overnight fast. Metabolic blood assays included fasting blood glucose (FBG), total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides (TG), insulin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transpeptidase (GGT), measured by clinical chemistry methods, on Advia XPT (Siemens Healthcare).

Triglyceride-glucose index (TyG index) was calculated as the $\ln[\text{fasting triglycerides (mg/dl)} \times \text{fasting plasma glucose (mg/dl)} / 2]$ (30), as a surrogate marker of IR and predictor of diabetes TyG index was considered pathological with a cutoff exceeding 7.88, according to Vieira Ribeiro (31).

Insulin resistance was determined by the homeostasis model assessment for insulin resistance (HOMA-IR) using the formula: $\text{insulin resistance} = (\text{insulin} \times \text{glucose}) / 22.5$ (32). Impaired insulin sensitivity was defined with HOMA-IR whenever exceeding the 97.5th percentile for age and sex and for Italian children and adolescents (33).

Statistical Analysis

The Shapiro-Wilk test was used to test the normal distribution of quantitative variables. As quantitative variables were normally distributed, the results were expressed as the mean value and standard deviation (SD). They were compared between BMI groups with ANOVA, followed by 2x2 post-hoc comparisons with Scheffé correction. Association between quantitative variables was evaluated with Pearson correlation, also stratifying for BMI groups and pubertal stage. The magnitude of an effect size for correlation coefficients should be evaluated as follows, according to Cohen (34): small for correlation coefficients on the order of 0.1; medium for those on the order of 0.3, large for those on the order of 0.5. We will focus on correlation coefficient in the order of 0.3 in line with many correlation coefficients reported in the literature (35).

Gender (M/F), pubertal stages were included as qualitative variables. Qualitative variables were summarized as counts and percentages and compared between groups with the chi-square test. The effect of TyG index on detection of insulin resistance was assessed using receiver operating characteristic (ROC) curves and the area under the ROC (AUROC) curve analysis. We also perform a non parametric analysis of ROC curve under covariates, using bootstrap to take into account the effect of BMI and pubertal stage.

All tests were two-sided and a p-value below 0.05 was considered statistically significant. The data analysis was performed with the STATA statistical package (release 15.1, 2017, Stata Corporation, College Station, Texas, USA)

Results

The features of the enrolled children according to BMI classification are reported in Table 1. Subjects with overweight and obesity compared to normal weight subjects showed significant differences in pubertal stage ($p < 0.05$) and components of the metabolic and cardiovascular profiles including insulin levels ($p < 0.001$), triglycerides and HDL cholesterol values ($p < 0.001$) and blood pressure ($p < 0.001$) (Tables 1, 2). There were no significant difference in gender and age between the groups.

In Table 3, we reported the percentile values of TyG index and HOMA-IR.

TyG index and clinical, metabolic and cardiovascular parameters

TyG index was more elevated in children with overweight and obesity compared to normal weight ($p < 0.001$ in both cases), Table 2. Gender and pubertal stage did not seem to influence the TyG index values, also considering stratification for BMI groups.

TyG index was statistically correlated with BMI ($r = 0.4$, $p < 0.001$), WHtR ($r = 0.36$, $p < 0.001$), total and HDL cholesterol ($r = 0.30$, $p < 0.001$ and $r = -0.32$, $p < 0.001$), ALT ($r = 0.22$, $p < 0.001$), systolic and diastolic pressure ($r = 0.22$, $p < 0.001$ and $r = 0.22$, $p < 0.001$).

As reported in Table 4, the correlation with TyG index remains significant for BMI, WHtR, HDL-cholesterol ALT also stratifying for pubertal stage and BMI group. For AST, after stratification, the correlation is revealed in overweight and obese children and pubertal stage 1 or 2. Regarding blood pressure, the systolic pressure remains correlated with TyG index, after stratification for pubertal stage and in children with obesity, while the diastolic pressure correlation with TyG was found in overweight and obese children and pubertal stage 1 or 2, Table 4.

HOMA-IR and clinical, metabolic and cardiovascular parameters

As reported in Table 2, HOMA-IR was higher in children with overweight and obesity than normal-weight ($p < 0.001$ in both cases), but no difference was shown between subjects with overweight compared to those with obesity ($p = 0.91$). No significant difference in HOMA-IR was found between group when sex was considered, also stratifying for BMI groups or pubertal stages.

Higher HOMA-IR values were noted in children with signs of puberty than prepubertal children ($p = 0.001$), without any difference related to sex between the groups, also when stratification for BMI groups was adopted.

Considering other auxological and metabolic parameters, HOMA-IR was correlated with BMI ($r = 0.41$, $p < 0.001$); WHtR ($r = 0.27$, $p < 0.001$), HDL-cholesterol ($r = -0.27$, $p < 0.001$); tryglicerides ($r = 0.31$, $p < 0.001$) and systolic blood pressure ($r = 0.2$, $p < 0.001$).

As reported in Table 5, these correlations remained significant for BMI, WHtR and HDL-cholesterol, even after stratification for pubertal stage and BMI group. Concerning blood pressure, the correlation resulted significant only in some groups, such as pubertal stage 2, normalweight and overweight, Table 5.

Correlation between TyG and HOMA-IR

Pathological TyG index and HOMA-IR were reported in 37.52% of subjects (7.89 % normal-weight, 48.27% overweight and 43.84 % with obesity) and 18.0 % (2.0 % normal-weight, 53.6% overweight and 44.4 % with obesity) respectively.

A correlation between TyG index and HOMA-IR ($r = 0.38$ $p < 0.001$) and elevated TyG index and pathological HOMA-IR ($p < 0.001$) were noted.

To reach the best sensitivity and specificity in the ROC analysis, 7.98 was considered optimal cutoff for insulin resistance by means of triglyceride-glucose index (sensitivity 60%; specificity 78%, AUC 0.69). Performing a nonparametric analysis, with bootstrap of ROC curve under covariates (pubertal stage and BMI) the AUC of the model was 0.70, Figure 1.

Discussion

Insulin resistance, characterized by a decrease in cell sensitivity to insulin, is one of the leading causes of metabolic abnormalities onset even at a young age, increasing the risk of cardiovascular diseases during adulthood (1, 36). It is important to identify simple and reliable predictors of IR for screening those at risk for MetS and T2DM.

Thus far, studies comparing predictors of IR in children and adolescents with obesity are limited (15-21). We detected a good sensitivity and specificity of the TyG index as a surrogate measure for predicting IR in children and adolescents with overweight/obesity. This index is correlated to abdominal obesity and dismetabolic profile, moreover, compared to HOMA-IR, it is not influenced by pubertal stage.

Although euglycemic-hyperinsulinemic clamp is the gold standard methods for the determination of insulin sensitivity, it is hardly practicable in children, being invasive and time intensive. Therefore, simpler, indirect methods have been proposed for epidemiological and clinical studies. HOMA- IR, derived from the product of the fasting levels of insulin and glucose, is a robust tool used as a surrogate measure for insulin resistance (4-8). Recently, Bonora *et al.* (37) reported a strong inverse correlation between clamp-measured glucose disposal and HOMA-estimated insulin sensitivity, suggesting that HOMA-IR can be reliably used in large-scale or epidemiological studies. Our results confirmed evidences that although TyG index has a high sensitivity and specificity towards IR prediction in pediatric population, it does not show any superiority of against HOMA-IR (6). TyG index is an alternative simple and inexpensive tool for identification of individuals at risk for IR (7, 38), such as children and adolescents with excessive weight gain or when insulin measurement is not available.

IR fluctuations throughout lifespan, with periods of expected physiological increases, such as puberty (39), complicates interpretation and assessment of IR in children. We noted that TyG index is not influence by puberty, therefore this marker may be also useful for screening IR in prepubertal and pubertal populations as well as in pediatric patients at high risk of dismetabolic disorders, with pubertal impairment, such as malnourished disabled children (40).

Metabolic syndrome (MetS) represents a clustering of metabolic risk factors including central obesity, hyperinsulinemia, hypertension, and dyslipidemia. Although the exact etiology of MetS is uncertain, IR is considered a common mechanism underlying derangements associated with the syndrome (2, 41). Thus, in order to delay or prevent the acute onset of these conditions, an early detection of IR, with accessible and easy-to-measure methods is recommended. Furthermore we noted a correlation between TyG index and other biomarkers for MetS, such as BMI, WHtR, total and HDL cholesterol, systolic and diastolic pressure and liver function. Despite, similarly to HOMA-IR, the correlation coefficients were low for some parameters. Moreover considering that in recent guidelines for pediatric obesity there are no specific recommends for fasting insulin measurement, TyG index, which is derived from fasting glucose and TG values, may be a reliable marker for this purpose. The difficulty of the formula with log, could be solved by an automatic calculation which would enable its practical use it in the clinical setting.

Reported data on cut-off values of TyG index to estimate IR for children and adolescents are limited. Veira Ribeiro *et al* (31) reported that the cutoff point with the best balance between sensitivity and specificity values was 7.88. A study carried out with Korean adolescents aged 10–18 identified cutoff points between 8.41 and 8.66 for TyG index to predict metabolic syndrome, using different diagnostic criteria (18). Angoorani *et al* (19) described a TyG-index cut-off of 8.33 in total students, as one of the indirect indices for metabolic syndrome in a pediatric population. Moon *et al* (16) reported cut-off values for TyG index between 8.45 and 8.65 in Mexican American, Non-Hispanic White, between 8.35 and 8.55 in Korean adolescents and between 8.15 and 8.35 in Non-Hispanic Black adolescents marker of IR and metabolic abnormalities.

The present study in Caucasian subjects identified an optimal cut-off of 7.98 for IR, that may be used for assessing IR and associated metabolic risk in children and teenagers with overweight and obesity, although caution is required when applied to other populations metabolically at risk.

A study limitation that should be acknowledged is the lack of dietary data. Dietary assessment of these patients is important since macronutrient composition impacts triglycerides levels. High carbohydrate diets raise blood concentrations of triglycerides. This “carbohydrate-induced hypertriglyceridemia” is paradoxical since dietary carbohydrates tend to increase plasma triglyceride when fats are displaced (42). Moreover trans fatty acids have been reported to increase triglyceride concentration, too. The major source of dietary trans fatty acids is partially-hydrogenated fats and products formulated with these fats such as commercially prepared baked

and fried foods, which children and adolescents are commonly fond of (42, 43). Finally weight history should be carefully investigated since triglycerides tend to lower during the active weight loss phase, regardless of nutrient composition (42); therefore children who have recently started a weight loss program and decreased weight, although still classified as overweight or obese, might reveal sudden changes in triglycerides levels, which do not necessarily mean a sudden improvement of IR. In **conclusion**, TyG index is a useful and cost-effective index of IR among children and adolescents. and it could be proposed also in different pathological populations, after validation. Additionally, TyG index role in insulin sensitivity estimation during recent fluctuations in weight and/or important dietary modifications is not excluded. The cutoff 7.98 may be used for IR risk screening in childhood obesity, but we recommend caution when used in other populations. Further studies, including correlation studies between TyG index and gold standard methods for insulin resistance, are needed to confirm the valid cut-off values in pediatrics.

Authorship Contributions

Medical Practices: Valeria Calcaterra, Daniela Larizza

Concept: Valeria Calcaterra, Hellas Cena

Design: Valeria Calcaterra, Hellas Cena

Data Collection or Processing: Corrado Regalbuto, Valeria Paganelli, Francesco Delle Cave, Chiara Montalbano, Riccardo Albertini

Analysis or Interpretation: Annalisa De Silvestri

Literature Search: Valeria Calcaterra, Corrado Regalbuto, Valeria Paganelli, Francesco Delle Cave, Chiara Montalbano

Writing: Valeria Calcaterra, Gloria Pelizzo, Daniela Larizza, Hellas Cena

All authors have read and approve of the manuscript.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Olson M, Chambers M, Shaibi G. Pediatric Markers of Adult Cardiovascular Disease. *Curr Pediatr Rev.* 2017;13:255-9.
2. Al-Hamad D, Raman V. Metabolic syndrome in children and adolescents. *Transl Pediatr.* 2017;6:397-07.
3. Kelley DE, Goodpaster BH 2001 Skeletal muscle triglyceride. An aspect of regional adiposity and insulin resistance. *Diabetes Care* 2001;24:933-41
4. Pan DA, Lillioja S, Kriketos AD, Milner MR, Baur LA, Bogardus C, Jenkins AB, Storlien LH. Skeletal muscle triglyceride levels are inversely related to insulin action. *Diabetes.* 1997;46:983-8.
5. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. *Diabetes Care.* 2004;27:1487-95.
6. Tohidi M, Baghbani-Oskouei A, Ahanchi NS, Azizi F, Hadaegh F. Fasting plasma glucose is a stronger predictor of diabetes than triglyceride-glucose index, triglycerides/high-density lipoprotein cholesterol, and homeostasis model assessment of insulin resistance: Tehran Lipid and Glucose Study. *Acta Diabetol.* 2018;55:1067-74.
7. Guerrero-Romero F, Simental-Mendía LE, González-Ortiz M, Martínez-Abundis E, Ramos-Zavala MAG, Hernández-González SO et al. The product of triglycerides and glucose, a simple measure of insulin sensitivity. Comparison with the euglycemic-hyperinsulinemic clamp. *J Clin Endocrinol Metabol* 2010;95:3347-51
8. Simental-Mendía LE, Rodríguez-Moran M, Guerrero-Romero F. The product of fasting glucose and triglycerides as surrogate for identifying insulin resistance in apparently healthy subjects. *Metab Syndr Relat Disord.* 2008;6:299-304.
9. Kang B, Yang Y, Lee EY, Yang HK, Kim HS, Lim SY, Lee JH, Lee SS, Suh BK, Yoon KH. Triglycerides/glucose index is a useful surrogate marker of insulin resistance among adolescents. *Int J Obes (Lond).* 2017;41:789-92
10. Er LK, Wu S, Chou HH, Hsu LA, Teng MS, Sun YC, Ko YL. Triglyceride Glucose-Body Mass Index Is a Simple and Clinically Useful Surrogate Marker for Insulin Resistance in Nondiabetic Individuals. *PLoS One.* 2016;11:e0149731.
11. Lee EY, Yang HK, Lee J, Kang B, Yang Y, Lee SH, et al. Triglyceride glucose index, a marker of insulin resistance, is associated with coronary artery stenosis in asymptomatic subjects with type 2 diabetes. *Lipids Health Dis.* 2016;15:155
12. Navarro-González D, Sánchez-Iñigo L, Pastrana-Delgado J, Fernández-Montero A, Martínez JA. Triglyceride-glucose index (TyG index) in comparison with fasting plasma glucose improved diabetes prediction in patients with normal fasting glucose: The Vascular-Metabolic CUN cohort. *Prev Med.* 2016 May;86:99-105. doi: 10.1016/j.ypmed.2016.01.022. Epub 2016 Feb 5.
13. Shimodaira M, Niwa T, Nakajima K, Kobayashi M, Hanyu N, Nakayama T. Serum triglyceride levels correlated with the rate of change in insulin secretion over two years in prediabetic subjects. *Ann Nutr Metab* 2014; 64: 38-43.
14. Freedman DS, Srinivasan SR, Harsha DW, Webber LS, Berenson GS. Relation of body fat patterning to lipid and lipoprotein concentrations in children and adolescents: the Bogalusa Heart Study. *Am J Clin Nutr* 1989; 50: 930-39.
15. Rodríguez-Moran M, Simental-Mendía LE, Guerrero-Romero F. The triglyceride and glucose index is useful for recognising insulin resistance in children. *Acta Paediatr.* 2017;106:979-83.
16. Moon S, Park JS, Ahn Y. The Cut-off Values of Triglycerides and Glucose Index for Metabolic Syndrome in American and Korean Adolescents. *J Korean Med Sci.* 2017;32:427-33.
17. Kang B, Yang Y, Lee EY, Yang HK, Kim HS, Lim SY, et al. Triglycerides/glucose index is a useful surrogate marker of insulin resistance among adolescents. *Int J Obes (Lond).* 2017;41:789-92.
18. Kim JW, Park SH, Kim Y, Im M, Han HS. The cutoff values of indirect indices for measuring insulin resistance for metabolic syndrome in Korean children and adolescents. *Ann Pediatr Endocrinol Metab.* 2016;21:143-8.
19. Angoorani P, Heshmat R, Ejtahed HS, Motlagh ME, Ziaodini H, Taheri M, et al. Validity of triglyceride-glucose index as an indicator for metabolic syndrome in children and adolescents: the CASPIAN-V study. *Eat Weight Disord.* 2018 Feb 16. doi: 10.1007/s40519-018-0488-z.
20. Cho J, Hong H, Park S, Kim S, Kang H. Insulin Resistance and Its Association with Metabolic Syndrome in Korean Children. *Biomed Res Int.* 2017;2017:8728017. doi: 10.1155/2017/8728017.
21. Simental-Mendía LE, Hernández-Ronquillo G, Gómez-Díaz R, Rodríguez-Morán M, Guerrero-Romero F. The triglycerides and glucose index is associated with cardiovascular risk factors in normal-weight children and adolescents. *Pediatr Res.* 2017;82:920-5.
22. Valerio G, Balsamo A, Baroni MG, Brufani C, Forziato C, Grugni G, et al. Childhood obesity classification systems and cardiometabolic risk factors: a comparison of the Italian, World Health Organization and International Obesity Task Force references. *Ital J Pediatr.* 2017;43:19.
23. Cacciari E, Milani S, Milani S, Balsamo A, Spada E, Bona G, Cavallo L, et al. Italian cross-sectional growth charts for height, weight and BMI (2-20 years). *J Endocrinol Invest* 2006;29:581-93.

24. Marshall WA, Tanner JM. Variations in patterns of pubertal changes in boys. *Arch Dis Child* 1969; 45: 13–23
25. Marshall WA, Tanner JM. Variations in patterns of pubertal changes in girls. *Arch Dis Child* 1969; 44: 291–303
26. Calcaterra V, De Amici M, Leonard MM, De Silvestri A, Pelizzo G, Buttari N, et al. Serum Calprotectin Level in Children: Marker of Obesity and its Metabolic Complications. *Ann Nutr Metab.* 2018;73:177-83.
27. Maffei C, Banzato C, Talamini G; Obesity Study Group of the Italian Society of Pediatric Endocrinology and Diabetology. Waist-to-height ratio, a useful index to identify high metabolic risk in overweight children. *J Pediatr* 2008; 152: 207-13.
28. Calcaterra V, De Giuseppe R, Biino G, Mantelli M, Marchini S, Bendotti G, Madè A, Avanzini MA, Montalbano C, Cossellu G, Larizza D, Cena H. Relation between circulating oxidized-LDL and metabolic syndrome in children with obesity: the role of hypertriglyceridemic waist phenotype. *J Pediatr Endocrinol Metab.* 2017;30:1257-63.
29. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents: The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics* 2004; 114: 555–576.
30. Simental-Mendía LE, Rodríguez-Morán M, Guerrero-Romero F. The product of fasting glucose and triglycerides as surrogate for identifying insulin resistance in apparently healthy subjects. *Metab Syndr Relat Disord.* 2008;6:299–304.
31. Vieira-Ribeiro SA, Fonseca PCA, Andreoli CS, Ribeiro AQ, Hermsdorff HHM, Pereira PF, Priore SE, Franceschini SCC. The TyG index cutoff point and its association with body adiposity and lifestyle in children. *J Pediatr (Rio J).* 2018 Feb 16. pii: S0021-7557(17)30443-6. doi: 10.1016/j.jped.2017.12.012.
32. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and β -cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985; 28: 412–9.
33. d'Annunzio G, Vanelli M, Pistorio A, Minuto N, Bergamino L, Iafusco D et al. Insulin resistance and secretion indexes in healthy Italian children and adolescents: a multicentre study. *Acta Biomedica* 2009; 80:21–8.
34. *Statistical Power Analysis for the Behavioral Sciences.* 2nd ed. Hillsdale, NJ: Lawrence Erlbaum Associates; 1988
35. Hemphill JF. Interpreting the magnitudes of correlation coefficients. *Am Psychol.* 2003;58:78–79
36. Namazi N, Djalalinia S, Mahdavi-Gorabi A, Asayesh H, Mansourian M, Noroozi M, Qorbani M. Association of wrist circumference with cardio-metabolic risk factors: a systematic review and meta-analysis. *Eat Weight Disord.* 2018 Jul 3. doi: 10.1007/s40519-018-0534-x.
37. Bonora E, Targher G, Alberiche M, Bonadonna RC, Saggiani F, Zenere MB, Monauni T, Muggeo M. Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity: studies in subjects with various degrees of glucose tolerance and insulin sensitivity. *Diabetes Care.* 2000;23:57-63.
38. Mohd Nor NS, Lee S, Bacha F, Tfayli H, Arslanian S. Triglyceride glucose index as a surrogate measure of insulin sensitivity in obese adolescents with normoglycemia, prediabetes, and type 2 diabetes mellitus: comparison with the hyperinsulinemic-euglycemic clamp. *Pediatr Diabetes.* 2016;17:458-65.
39. Pilia S, Casini MR, Foschini ML, Minerba L, Musiu MC, Marras V, Civolani P, Loche S. The effect of puberty on insulin resistance in obese children. *J Endocrinol Invest.* 2009 May;32(5):401-5
40. Pelizzo G, Calcaterra V, Carlini V, Fusillo M, Manuelli M, Klersy C, et al. Nutritional status and metabolic profile in neurologically impaired pediatric surgical patients. *J Pediatr Endocrinol Metab.* 2017;30:289-300.
41. Higgins V, Adeli K. Pediatric Metabolic Syndrome: Pathophysiology and Laboratory Assessment. *EJIFCC.* 2017 Mar 8;28:25-42.
42. Parks Elizabeth J.; Effect of Dietary Carbohydrate on Triglyceride Metabolism in Humans, *The Journal of Nutrition*, 2001; 131: 2772S–2774S
43. Lichtenstein Alice H. Dietary Fat, Carbohydrate and Protein: Effects on Plasma Lipoprotein Profiles Fat, Carbohydrate and Protein and Plasma Lipids. *J.of Lipid Research*, 2018. *J Lipid Res.* 2006;47:1661-7

Table 1. Clinical features of the enrolled children.

	All (n=541)	Normal weight (n=120)	Overweight (n=221)	Obese (n=200)
Age (yrs)	11.70±2.71	11.23±2.66	11.77±2.55	11.90±2.89
Gender (M/F)	275/266	61/59	108/113	106/94
Pubertal stage#				
Stage 1	116	33	41	42
Stage 2	281	66	124	91
Stage 3	144	21	56	67
Height (cm)*	149.99±14.24	144.74±14.15	151.11±13.43	151.91±14.47
Weight (kg)*	56.42±19.72	37.99±11.66	59.93±18.12	63.61±18.46
Body Mass Index (kg/m ²)	24.40±5.46	17.66±2.57	25.69±4.51	27.03±4.28
Waist to height ratio **	0.52±0.07	0.43±0.04	0.54±0.06	0.56±0.05
Diastolic pressure (mmHg)*	67.49±8.49	63.81±8.62	68.58±8.28	68.50±8.06
Systolic pressure (mmHg)*	107.57±11.65	102.40±10.23	108.61±11.43	109.52±11.85

#p<0.05 of obese and overweight vs control; *p<0.001 of obese and overweight vs control; **p<0.001 of obese and overweight vs control and p=0.003 between obese and overweight; §p<0.01 of obese and overweight vs control

Table 2. Biochemical parameters of the enrolled children.

	All (n=541)	Normal weight (n=120)	Overweight (n=221)	Obese (n=200)
Fasting blood glucose (mg/dl)	76.13±9.28	74.80±8.25	76.20±9.46	76.86±9.61
Insulin (mU/ml)*	11.92±10.31	6.32±4.28	13.42±10.54	13.50±11.38
HOMA-IR*	1.81±1.89	0.90±1.05	2.10±1.89	2.03±2.11
Triglycerides (mg/dl)*	69.60±35.91	51.30±21.47	73.61±37.28	76.15±37.73
Total Cholesterol (mg/dl)	160.20±28.12	156.57±27.42	161.33±26.29	160.95±30.34
HDL-Cholesterol (mg/dl)*	49.30±10.70	54.49±10.68	48.35±10.21	47.50±10.37
Triglyceride -glucose index*	7.76±0.46	7.48±0.39	7.82±0.44	7.87±0.45
AST (mU/ml)	22.10±7.49	23.62±5.96	22.05±8.04	21.36±7.50
ALT (mU/ml)§	20.73±15.53	15.67±5.59	21.99±17.86	22.07±15.92
GGT (mU/ml)§	17.45±12.87	13.04±4.80	18.66±14.73	18.31±13.28

HOMA-IR: homeostasis model assessment-insulin resistance; AST: asparase aminotransferase; ALT: alanine aminotransferase; GGT: gamma glutamyl transpeptidase

#p<0.05 of obese and overweight vs control; *p<0.001 of obese and overweight vs control; **p<0.001 of obese and overweight vs control and p=0.003 between obese and overweight; §p<0.01 of obese and overweight vs control

Table 3. Percentile values of Triglyceride-glucose index (TyG index) and homeostasis model assessment for insulin resistance (HOMA-IR)

Percentiles	TyG index	HOMA-IR
1%	6.887553	.0831215
5%	7.120848	.2116522
10%	7.226936	.3398203
25%	7.447751	.6122222
50%	7.705262	1.281852
75%	8.009031	2.30321
90%	8.369157	3.935556
95%	8.628198	5.44642
99%	9.052809	9.819753

Uncorrected proof

Table 4. Correlation between TyG and clinical, metabolic and cardiovascular parameters stratifying for pubertal stage and BMI

Parameters	Triglyceride -glucose index*					
	Pubertal Stage 0	Pubertal Stage 1	Pubertal stage 2	Normalweight	Overweight	Obese
Body mass index r p	0.333 0,0003	0.4419 <0.001	0.3517 <0.001	0.1737 0,0478	0.3508 <0.001	0.1826 0.0096
Waist to height ratio r p	0.3262 0.0004	0.3826 <0.001	0.4181 <0.001	0.2661 0.0033	0.2137 0.0014	0.2002 0.0045
HDL-Cholesterol r p	-0,1883 0.0499	-0.347 <0.001	-0.3748 <0.001	-0.0957 0.3199	-0.3172 <0.001	-0.3163 <0.0010
Total Cholesterol r p	0,2397 0.0121	0.3535 <0.001	0,3016 0,0003	0.2766 0,0034	0.3601 <0.001	0.2378 0.0007
Triglycerides r p	0.9028 <0.001	0.9332 <0.001	0.9184 <0.001	0.9155 <0.001	0.9184 <0.001	0.935 <0.001
AST r p	0.1141 0.2376	0.0754 0.2132	0.1783 0.0371	-0.116 0.2365	0.2194 0.0011	0.1231 0.0831
ALT r p	0.2002 0.036	0.2433 <0.001	0.228 0.0074	-0.065 0.5039	0.2745 <0.001	0.1449 0.0411
GGT r p	0.0777 0.4198	0.1327 0.0278	0.2861 0.0007	0.161 0.0959	0.0807 0.2333	0.1291 0.0691
Systolic pressure r p	0.2038 0.0289	0.2052 0.0006	0.1853 0.0284	0.1347 0.1442	0.2406 0.0003	0.0822 0.2471
Diastolic pressure r p	0.1783 0.0576	0.2601 <0.001	0.1097 0.1969	0.1704 0.0639	0.2573 0.0001	0.0526 0.4597

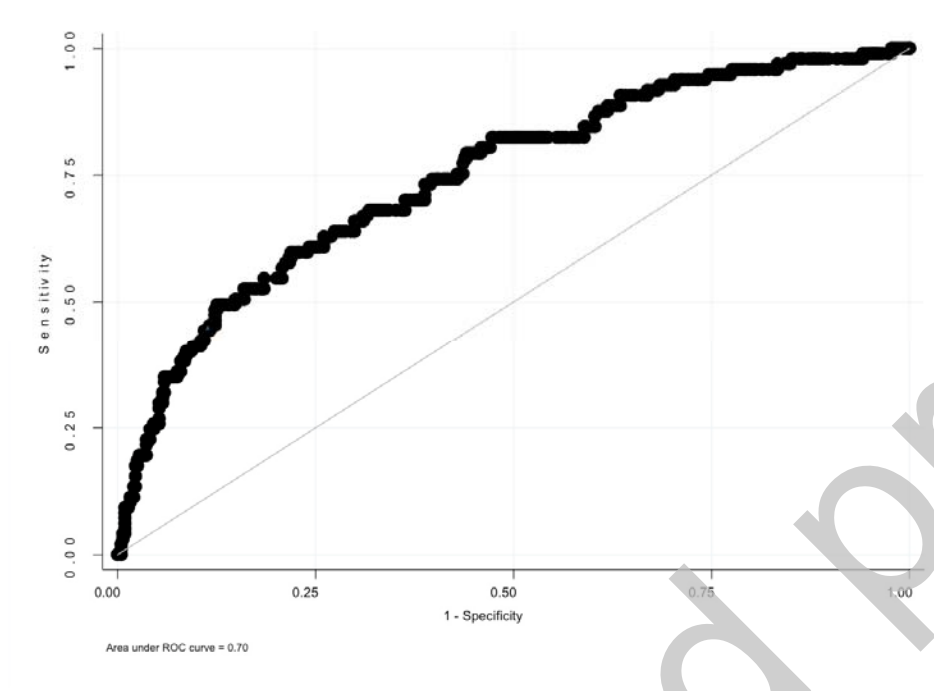
HOMA-IR: homeostasis model assessment-insulin resistance; AST: asparase aminotransferase; ALT: alanine aminotransferase; GGT: gamma glutamyl transpeptidase; Pubertal stage 1 = Tanner 1; Pubertal stage 2 = Tanner 2–3 and Pubertal stage 3 = Tanner 4–5

Table 5. Correlation between HOMA-IR and clinical, metabolic and cardiovascular parameters stratifying for pubertal stage and BMI

Parameters	HOMA-IR					
	Pubertal Stage 0	Pubertal Stage 1	Pubertal stage 2	Normalweight	Overweight	Obese
Body mass index r p	0.3056 0.0009	0.4291 <0.001	0.3841 <0.001	0.4092 <0.001	0.1739 <0.001	0.5292 <0.001
Waist to height ratio r p	0.2547 0.006	0.2799 <0.001	0.3231 0.0001	0.5079 <0.001	-0.0607 0.3691	0.3203 <0.001
HDL-Cholesterol r p	-0.2323 0.0151	-0.2918 <0.001	-0.2327 0.006	-0.1804 0.0617	-0.2508 0.0002	-0.233 0.001
Total Cholesterol r p	-0.0505 0.6021	0.0863 0.1534	0.0466 0.5876	-0.0112 0.9082	-0.0005 0.9947	0.0433 0.5449
Triglycerides r p	0.1379 0.1415	0.3456 <0.001	0.3563 <0.001	0.3363 0.0002	0.242 0.0003	0.2783 0.0001
AST r p	-0.1244 0.1975	0.0212 0.7277	0.255 0.0026	-0.2383 0.0144	0.1325 0.0496	0.0676 0.3443
ALT r p	0.1258 0.1905	0.21 0.0005	0.1733 0.0428	0.0327 0.7379	0.173 0.0101	0.1336 0.0606
GGT r p	0.0846 0.3793	0.0462 0.447	0.1904 0.0258	0.0713 0.4655	0.0174 0.7971	0.0667 0.3504
Systolic pressure r p	0.1723 0.0668	0.2262 0.0002	0.0441 0.6048	0.2186 0.0189	0.1932 0.0041	0.1083 0.1277
Diastolic pressure r p	0.0529 0.5777	0.176 0.0035	0.0561 0.5102	0.1921 0.0397	0.1324 0.0508	0.085 0.2326

HOMA-IR: homeostasis model assessment-insulin resistance; AST: asparase aminotransferase; ALT: alanine aminotransferase; GGT: gamma glutamyl transpeptidase; Pubertal stage 1 = Tanner 1; Pubertal stage 2 = Tanner 2–3 and Pubertal stage 3 = Tanner 4–5

Figure 1 Area under the ROC of the effect of TyG index on detection of insulin resistance



Uncorrected proof