

Triglycerides-to-HDL cholesterol ratio as screening tool for impaired glucose tolerance in obese children and adolescents

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Abstract

Aims To identify metabolic phenotypes at increased risk of impaired glucose tolerance (IGT) in Italian overweight/obese children ($n = 148$, age 5–10 years) and adolescents ($n = 531$, age 10–17.9 year).

Methods Phenotypes were defined as follows: obesity by the 95th cut-points of the Center for Disease Control body mass index reference standards, impaired fasting glucose (fasting plasma glucose ≥ 100 mg/dl), high circulating triglycerides (TG), TG/HDL cholesterol ≥ 2.2 , waist-to-height ratio (WTHR) > 0.6 , and combination of the latter with high TG or TG/HDL cholesterol ≥ 2.2 .

Results In the 148 obese children, TG/HDL-C ≥ 2.2 (OR 20.19; 95 % CI 2.50–163.28, $p = 0.005$) and the combination of TG/HDL-C ≥ 2.2 and WTHR > 0.60 (OR 14.97; 95 % CI 2.18–102.76, $p = 0.006$) were significantly

associated with IGT. In the 531 adolescents, TG/HDL-C ≥ 2.2 (OR 1.991; 95 % CI 1.243–3.191, $p = 0.004$) and the combination with WTHR > 0.60 (OR 2.24; 95 % CI 1.29–3.87, $p = 0.004$) were associated with significantly increased risk of IGT. In the whole sample, having high TG levels according to the NIH National Heart, Lung and Blood Institute Expert Panel was not associated with an increased risk of presenting IGT.

Conclusions TG/HDL-C ratio can be useful, particularly in children, to identify obese young patients at risk of IGT. Its accuracy as screening tool in a general population needs to be verified. The combination of TG/HDL-C ratio and WTHR > 0.6 did not improve prediction. Having high TG according to the NIH definition was not associated with increased risk of developing IGT.

Keywords Children · Impaired glucose tolerance · Pediatric obesity · Triglycerides-to-HDL cholesterol ratio · Waist

Managed by Massimo Porta.

On the behalf of the Childhood Obesity Group of the Italian Society of Paediatric Endocrinology and Diabetology. See study members referred in “Appendix” section.

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Abbreviations

BMI	Body mass index
BP	Blood pressure
FBG	Fasting blood glucose
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
HDL-C	High-density lipoprotein cholesterol
OGTT	Oral glucose tolerance test
T2D	Type 2 diabetes
TG/HDL-C	Triglycerides-to-HDL cholesterol ratio
WTHR	Waist-to-height ratio

Introduction

The increasing prevalence of childhood obesity in westernized and developing countries adds new concerns for healthcare providers. Its impact on type 2 diabetes (T2D) is one major point [1].

When severe enough, obesity might anticipate the onset of pre-diabetes (i.e., impaired fasting glucose, IFG, and impaired glucose tolerance, IGT) to teen age and full-blown T2D to early adulthood. In the USA, 20–30 % of obese youth have “pre-diabetes” as a condition of marked insulin resistance (IR) and β -cell dysfunction [2]. IFG seems resulting from an impaired first-phase insulin secretion, indicating both dysfunctional β -cell activity and increased hepatic IR. IGT arises from impaired β -cell glucose sensitivity that leads to defective first-phase secretion in the long run [3]. By placing an increased demand on the β -cell to hypersecrete insulin, IR influences the progressive β -cell failure up to the development of IGT first, and T2D later on [4]. Obese children and adolescents of both genders show increased IR at any age [5]. General awareness of pre-diabetes and diabetes in youth has developed during the last decade. The American Diabetes Association (ADA) recommends screening at-risk adolescents (i.e., those with severe IR) using the fasting plasma glucose (FPG) or the oral glucose tolerance test (OGTT) every 2 years starting at 10 years of age or at the onset of puberty. The ADA specifies that if FPG is impaired (FPG \geq 100 mg/dl), additional diagnostic testing with an OGTT is recommended [6]. Albeit preferred for practical reasons, the FPG is less sensitive than the OGTT because it cannot identify all the individuals with IGT that, worth mentioning, is the strongest predictor of T2D in youth [7]. Studies described FPG as poor predictor of IGT [2, 8–14]. Two of studies recommended adding serum triglyceride (TG) concentrations to FPG to improve the accuracy to detect IGT cases [11, 13]. One study investigated the ability of the product of FPG per TG to predict T2D. The performance of such product was, however, poorer as

compared to the performance of 1- and 2-h plasma glucose [14].

Findings from the Early Bird study suggest that the decline of insulin sensitivity in children begins years before the puberty [15] and it is more severe in low-birth-weight children who rapidly gain body weight during the early postnatal years as found by the Avon longitudinal study of pregnancy and childhood study [16]. Smaller size at birth, lower IGF-I levels, and childhood height are associated with reduced compensatory insulin secretion [16]. The combination of severely increased IR and the impaired β -cell response may cause IGT even before 10 years of age in severely obese children [17]. Hence, the identification of phenotypes at increased risk of IGT in children (<10 years of age) might be useful in the clinical practice.

For this purpose, we tried to identify metabolic phenotypes among high abdominal adiposity, impaired fasting glucose (IFG), high TG, low HDL-C, or high TG-to-HDL cholesterol ratio (TG/HDL-C) that best predict IGT in a sample of 679 Italian obese children (age <10 years) and adolescents (age \geq 10 years of age). In addition, phenotypes combining high TG or high TG/HDL-C to high abdominal adiposity were assessed. Abdominal adiposity was estimated as waist-to-height ratio (WTHR) instead of waist circumference to avoid use of specific population percentiles.

Research design and methods

Between January 2005–December 2009, eight pediatric obesity services participated in a retrospective cross-sectional study, providing medical records of 679 outpatient obese children and adolescents who underwent clinical examination, fasting blood analysis, and OGTT. Inclusion criteria were: Caucasian race, age (5–17.9 years), and having complete data set as elsewhere described [18]. Exclusion criteria were: secondary obesity, chronic diseases, malformations and chronic use of drugs causing metabolic disturbances, and 2-h blood glucose >200 mg/dl (OGTT).

The study protocol was approved by the Childhood Obesity Group Review Board of the Italian Society for Paediatric Endocrinology and Diabetology (SIEDP). It conformed to the guidelines of the European Convention of Human Rights and Biomedicine for Research in Children. All measures were taken to ensure the confidentiality of families and children whose data were used. Patient's personal and clinical data were anonymized before transmission and analysis. The directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of personal data was complied with for data storage and handling.

Anthropometry and blood pressure evaluation

Body weight and height were measured in each center by the same investigator, who was specifically trained in anthropometry according to SIEDP guidelines [18]; the average of the two closest measurements of height was used for the analysis; if a difference of 0.5 cm or more was found, a third measurement was taken. The BMI was calculated as weight divided by square of height (kg/m^2). Waist circumference was measured using a flexible tape at the midpoint between the last rib and the iliac crest at minimal respiration when the participant was in a standing position. The WTHR was calculated (waist circumference in centimeters divided by height in centimeters). Blood pressure (BP) was measured according to standard procedures [19]. Briefly, BP was measured at the right arm in the sitting position after a 5-min rest, using an aneroid sphygmomanometer with an appropriately sized cuff; three readings were taken 2 min apart, and the average of the two last values was used in the analyses.

The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using the formula $\text{HOMA-IR} = [\text{glucose (nmol/L)} * \text{insulin } (\mu\text{U/mL})/22.5]$.

Biochemical parameters

Fasting TG were measured enzymatically, the HDL-C fraction was obtained after precipitation using a phosphotungstic reagent, and glucose was measured using a glucose oxidase method. Although analyses were performed in different laboratories, all centers belong to the Italian National Health system and are certified according to International Standards ISO 9000 (www.iso9000.it/), undergoing semi-annual quality controls and inter-laboratory comparisons; this contributes to limit the potential differences among laboratories.

Definition of phenotypes at increased risk of IGT

Obesity was defined by the 95th cut-points of the Center for Disease Control (CDC) BMI reference standards [20]. BMI values were transformed into standard deviation scores (SDS), based upon the CDC established normative curves [20].

The following cardiometabolic risk factors were considered: WTHR ≥ 0.6 as index of central adiposity [21]; high BP (HBP), defined by systolic (SBP) and/or diastolic (DBP) blood pressure ≥ 95 th percentile for age, sex, and height [19]; high TG levels, defined using the cutoff ≥ 100 mg/dl (children 0–9 years) or ≥ 130 mg/dl (adolescents 10–19 years) as proposed by the Expert Panel Definition [19]; low HDL-C levels, defined by values < 40 mg/dl [19]; TG/HDL-C ≥ 2.2 as a marker of atherogenic lipid

profile [22, 23]; IFG as glucose ≥ 100 mg/dl; and IGT as 2 h glucose ≥ 140 mg/dl following the OGTT [6]. The hypertriglyceridemic WTHR phenotype was defined as TG ≥ 100 mg/dl (children 0–9 years) or ≥ 130 mg/dl (adolescents 10–19 years) and WTHR ≥ 0.60 , while the combined dyslipidemic WTHR phenotype was defined as TG/HDL-C ≥ 2.2 and WTHR ≥ 0.60 .

Statistical analysis

Continuous data are reported as means and standard deviations (SD), with categorical data as count and percentage. Variables were not normally distributed (except age, weight, and BMI-SDS). The general linear model was used to determine whether the means between IGT and no IGT groups differed, controlling by age, sex, and center. Contingency tables were used for categorical variables.

Odds ratio (OR) associated with IGT was calculated using multiple logistic analysis, controlled for major confounding factors (centers, gender, and BMI-SDS).

The Statistical Package of Social Sciences (SPSS, Chicago, IL, USA) for Windows software program release 18.0 was used. A p value < 0.05 was considered significant.

Results

The whole sample included 302 males (44.5 %), 148 children (22.6 %), and 531 (77.4 %) adolescents. IGT was found in nine children (6.0 %) and 67 adolescents (12.6 %). Table 1 describes characteristics of obese patients with ($n = 76$; 11 %) and without IGT ($n = 603$; 89 %). Significant differences were observed in BMI and visceral adiposity, FPG, IR as estimated by the HOMA-IR, TG, TG/HDL-C ratio, SBP, and DBP (p ranging from 0.007 to < 0.0001). IFG was found in six (8 %) IGT versus 28 (5 %) non-IGT patients ($p = 0.2$); WTHR > 0.6 in 68 (90 %) IGT versus 367 (61 %) non-IGT subjects ($p < 0.0001$); high TG levels in 18 (24 %) versus 110 (18 %) ($p = 0.25$); low HDL-C in 27 (36 %) versus 160 (27 %) ($p = 0.09$); TG/HDL-C ≥ 2.2 in 46 (61 %) and 209 (35 %) ($p < 0.0001$); high BP in 37 (49 %) versus 245 (41 %), $p = 0.2$; the combination of the WTHR > 0.6 and high TG in 17 (22 %) and 66 (11 %) ($p = 0.004$); and the combination of WTHR > 0.6 and TG/HDL-C ≥ 2.2 in 40 IGT (53 %) and 136 non-IGT (23 %) patients ($p < 0.0001$). When comparing IGT versus non-IGT obese patients and taking into account the two classes of age (Table 2), the prevalence of high TG tended to be different in children but not in adolescents. The prevalence of both high TG levels and WTHR > 0.6 was significantly higher ($p = 0.004$) in children but not in adolescents ($p = 0.06$). Phenotypes of WTHR > 0.6 , TG/HDL-C ≥ 2.2 , and their

Table 1 Features of children and adolescents according to IGT status

	No IGT	IGT	<i>p</i> value
<i>n</i> = 679 (%)	603 (89)	76 (11)	
Age (years)	13 ± 3	14 ± 3	0.001
Boys <i>n</i> (%)	267 (44)	35 (46)	0.769
BMI (kg/m ²)	33 ± 6	38 ± 7	<0.0001
BMI-SDS	2.33 ± 0.33	2.53 ± 0.29	<0.0001
WTHR	0.64 ± 0.09	0.70 ± 0.09	<0.0001
FPG (mg/dl)	83 ± 10	86 ± 11	0.006
HOMA-IR	3.1 ± 2.0	4.1 ± 2.5	<0.0001
TG (mg/dl)	92 ± 46	118 ± 55	<0.0001
HDL-C (mg/dl)	46 ± 11	44 ± 11	0.118
TG/HDL-C ratio	2.2 ± 1.5	2.9 ± 1.7	<0.0001
SBP (mmHg)	121 ± 14	127 ± 12	<0.032
DBP (mmHg)	74 ± 10	80 ± 10	<0.004

Data are expressed as mean ± SD, *n* (%)

BMI body mass index, *BMI-SDS* body mass index standard deviation score, *WC* waist circumference, *WTHR* waist-to-height ratio, *FPG* fasting plasma glucose, *HOMA-IR* homeostasis model assessment of insulin resistance, *TG* triglycerides, *HDL-C* HDL cholesterol, *SBP* systolic blood pressure, *DBP* diastolic blood pressure

combination were significantly more prevalent in IGT children and adolescents than in non-IGT peers (*p* ranging from 0.03 to <0.0001).

Table 3 reports the ORs estimating the risk of IGT associated with different metabolic phenotypes in the whole population and in the two age groups (adjusted for centers, gender, and BMI-SDS).

Discussion

Findings of our study suggest that the TG/HDL cholesterol ≥ 2.2 is the phenotype best predicting the risk of IGT in the youth. It seems working better in children than in

adolescents. The combination of the WTHR >0.6 to the TG/HDL cholesterol did not improve the performance of the latter. Of note, the hypertriglyceridemic phenotype, defined by the criteria of the NIH National Heart, Lung and Blood Institute Expert Panel, was not associated with an increased risk of IGT even when combined to the WTHR >0.6 .

The prevalence of IGT and diabetes in young Italian patients affected by severe obesity is not so high [24] as reported in US obese youth by the SEARCH for Diabetes in youth study [25]. In our series, one adolescent solo was diagnosed with T2D (prevalence of 0.14 %) and excluded from the analysis. The prevalence of impaired glucose metabolism was significantly lower than that reported by the SEARCH study in white Americans [25]. These different figures in white youth may be due to differences in obesity rates between US and European Caucasians populations; in exposure to prenatal (nutritional cues and endocrine-disrupting chemicals in utero) and early postal factors [16]; and to frequent single nucleotide polymorphisms but with small phenotypic effect or relatively rare variants with larger effects whose frequencies vary also in people of same ethnicity (in this case all Caucasians) but different ancestry [26]. In front of such heterogeneity of causative factors, there is need of specifically population-tailored models predicting the risk of impaired glucose metabolism [27].

The TG/HDL-C ratio ≥ 2.2 has been very recently confirmed as accurate screening tool identifying IR, high blood pressure, metabolic syndrome, liver steatosis, higher carotid intima-media thickness, and concentric left ventricular hypertrophy in the 5505 children and adolescents from the “Cardiometabolic risk factors in overweight and obese children in Italy” (CARITALY) study [23]. Previously, Weiss et al. [28] demonstrated the association of a high TG/HDL-C in adolescence with development of a

Table 2 Proportions of children and adolescents with cardiometabolic risk factors according to IGT status and age class

	Age <10 years			Age ≥ 10 years		
	No IGT 139	IGT 9	<i>p</i> value	No IGT 464	IGT 67	<i>p</i> value
IFG	8 (6)	3 (33)	0.002	20 (4)	3 (5)	1.000
WTHR > 0.6	57 (41)	7 (78)	0.031	310 (67)	61 (91)	<0.0001
High TG ^a	35 (25)	5 (56)	0.06	75 (16)	13 (19)	0.505
Low HDL-C ^a	25 (18)	3 (33)	0.372	135 (29)	24 (36)	0.261
TG/HDL-C ≥ 2.2	38 (27)	7 (78)	0.004	171 (37)	39 (58)	0.001
High BP	44 (32)	6 (67)	0.062	201 (43)	31 (46)	0.649
WTHR > 0.6 and high TG ^a	19 (14)	5 (56)	0.004	47 (10)	12 (18)	0.063
WTHR > 0.6 and TG/HDL-C ≥ 2.2	17 (12)	6 (67)	<0.0001	119 (26)	34 (51)	<0.0001

IFG impaired fasting glucose, *WTHR* waist-to-height ratio, *TG* triglycerides, *HDL-C* HDL cholesterol, *BP* blood pressure

^a High TG and low HDL-C according to the Expert Panel Definition [16]

Table 3 Odds ratios adjusted for centers, gender, and BMI z-score of cardiometabolic phenotypes associated with IGT in the whole sample and in the two groups of age

	Whole sample (n = 679)		Children (n = 148)		Adolescents (n = 531)	
	OR (95 % CI)	p value	OR (95 % CI)	p value	OR (95 % CI)	p value
WTHR > 0.6	1.81 (0.71–4.57)	0.212	2.16 (0.32–14.75)	0.433	1.08 (0.36–3.26)	0.887
TG/HDL \geq 2.2	2.63 (1.57–4.39)	<0.0001	20.19 (2.50–163.28)	0.005	2.24 (1.29–3.87)	0.004
WTHR and high TG ^a	1.64 (0.98–2.71)	0.051	2.74 (0.83–8.98)	0.097	1.25 (0.69–2.27)	0.470
WTHR > 0.6 and TG/HDL \geq 2.2	2.49 (1.48–4.19)	0.001	14.97 (2.18–102.76)	0.006	1.95 (1.11–3.41)	0.020

WTHR Waist-to-height ratio, TG/HDL triglycerides-to-HDL cholesterol ratio

^a High triglycerides according to the Expert Panel Definition [16]

proatherogenic lipid profile later in young adulthood. In a study of 1452 obese youths, the TG/HDL-C ratio was associated with IR mainly in white obese boys and girls, but not in Hispanics and African-Americans individuals, again confirming the need of population-specific predictive model of risk [27]. Furthermore, these predictive models in young patients must take into account also pubertal development, which is well known to affect IR. Unfortunately, this information was missed in our series. However, we run all the regression models controlling for age.

As to other investigated phenotypes, previous studies tested the accuracy of FPG to predict IGT [29, 30]. Studies investigated the performance of risk phenotypes associated with the worsening of IR (i.e., greater whole body fatness as estimated by the BMI, visceral adiposity, high levels of fasting TG, and low levels of HDL-C, fasting state free fatty acids (FFAs), FFAs during an OGTT, and overnight FFAs among others) [31, 32]. Values of FPG ranging from 75 to 95 mg/dl in association with classes of TG as high as 80 mg/dl to 120 mg/dl were found to predict IGT with good accuracy [29]. In a clinic-based Canadian population of 256 obese children and adolescents (age ranging from 5 to 17 years of age) with a 13.9 % prevalence of IGT, a fasting TG concentration >1.17 mmol/l (104 mg/dl) was proposed as a simple clinical criterion for selecting obese children who deserve OGTT (71.4 % sensitivity, 64.1 % specificity for isolated IGT) [33].

The association of high circulating TG and waist circumference has been known for a long time as metabolic risk factor efficiently predicting cardiovascular disease and T2D in adults [34]. In the pediatric population, cutoff points of fasting TG and waist circumferences to define a combined phenotype of risk may result cumbersome since their values vary physiologically based on ethnicity, gender, and age. The use of the TG/HDL-C allows overcoming the use of specific population percentiles, being TG and HDL-C routinely estimated in the clinical practice, and also importantly economically affordable on large scale. It

is worth noting that our results were obtained in a sample of obese patients enrolled in secondary healthcare centers and, they need to be verified in a general population.

In conclusion, findings of the present investigation support the reliability of the TG/HDL-C ratio to predict the risk of IGT in both obese children and adolescents. The risk of IGT associated with the TG/HDL-C ratio \geq 2.2 was extremely high in children as compared to adolescents.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standard All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Human and animal rights disclosure All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Informed consent Informed consent was obtained from all patients for being included in the study.

Appendix

Childhood Obesity Group of the Italian Society of Paediatric Endocrinology and Diabetology: Nicola Corciulo, MD, Ospedale S. Cuore di Gesù Gallipoli, Lecce; Maria Rosaria Licenziati, MD, Dipartimento di Pediatria, AORN Santobono-Pausilipon, Napoli. Anita Morandi, MD, Pediatria ad Indirizzo Diabetologico e Malattie del Metabolismo, Università di Verona, Verona; Beatrice Moro, MD, Ospedale Civile Piove di Sacco, Padova; Alessandro Sartorio, MD, Divisione di Auxologia, Istituto Auxologico Italiano, Piancavallo, Verbania; Rita Tanas, MD, Azienda Ospedaliero-Universitaria Arcispedale S. Anna, Ferrara.

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