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ORIGINAL ARTICLE

Oral glucose effectiveness and metabolic risk in obese children and adolescents

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Abstract

Aim To investigate whether GE is affected in children/adolescents with obesity and abnormalities of the metabolic syndrome (MetS).

Methods Cross-sectional study of oral GE (oGE), insulin sensitivity and secretion (calculated on 5 time-points oral glucose tolerance test) and metabolic abnormalities in 1012 patients with overweight/obesity (aged 6.0–17.9 years old). A MetS risk score was calculated on the basis of distribution of fasting glucose, triglycerides, HDL-cholesterol, total cholesterol, systolic and diastolic blood pressure. Non-alcoholic fatty liver disease (NAFLD) was suspected based on thresholds of alanine aminotransferases.

Results Four-hundred and eighty patients (47.73%) had low-MetS risk score, 488 medium (48.22% with 1–2 risk factors) and 41 (4.05% with ≥ 3 factors) high risk. oGE was significantly lower in subjects with obesity [3.81 (1.46) mg/dl/min^{-1}] than in those with overweight [4.98 (1.66) mg/dl/min^{-1}; p value < 0.001]. oGE was negatively correlated with BMI ($\rho = -0.79$; $p < 0.001$) and BMI z score ($\rho = -0.56$; $p < 0.001$) and decreased significantly among MetS risk classes ($p = 0.001$). The median difference of oGE from low to medium risk was estimated to be as −4.9%, from medium to high as −13.38% and from low to high as −17.62%. oGE was not statistically different between NAFLD+ and NAFLD− cases.

Conclusions In children and adolescents with obesity oGE decreases. Noteworthy, it decreases as the Met score increases. Therefore, reduced oGE may contribute to the higher risk of these individuals to develop type 2 diabetes.

Keywords Glucose effectiveness · Glucose metabolism · Metabolic syndrome

Abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under curve
BMI	Body mass index
EHC	Euglycemic Hyperinsulinemic Clamp
HDL-cholesterol	High-density lipoprotein cholesterol
HGP	Hepatic glucose production
HIRI	Hepatic Insulin Resistance Index
HOMA-IR	Homeostasis model assessment for insulin resistance
IVGTT	Intravenous glucose tolerance test
ISI	Insulin sensitivity index
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
IR	Insulin resistance
MetS	Metabolic syndrome
NAFLD	Non-alcoholic fatty liver disease
NGT	Normal glucose tolerance
oDI	Oral disposition index
OGTT	Oral glucose tolerance test
T2D	Type 2 diabetes
TG	Triglycerides

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Introduction

Epidemic obesity in children is associated with the development of comorbidities previously considered to be "adult" diseases, i.e. prediabetes and type 2 diabetes (T2D). Prediabetes encompasses impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) [1].

Three major factors contribute to maintain glucose homeostasis in fasting condition and normalize glucose levels after either oral glucose tolerance test (OGTT) or intravenous glucose challenge. The insulin sensitivity is the ability of insulin to promote the entry of glucose into cells and to suppress the hepatic glucose production (HGP). The β-cell function conveys the amount and dynamics of insulin secretion. Glucose effectiveness (GE) expresses the capability of glucose itself to stimulate its own uptake and to suppress HGP independently of insulin [2–5].

With regard to the pathophysiology of impaired glucose metabolism in obese children, most studies focused on the dramatic worsening of peripheral insulin sensitivity owing to the obesity condition. Some of them highlighted the reduced responsiveness of the β-cell to compensate for the increased insulin demand as the main mechanism leading to IGT and T2D in insulin-resistant youngsters with obesity [revised in 6, 7]. Very few studies quantified the contribution of an inadequate HGP suppression [8–13]. Even fewer studies investigated the pathogenetic role of GE [8, 14–16].

In fasted glucose-tolerant adults, GE contributes to 70% of glucose disposal [17], while the hepatic effect accounts for the remaining 30% [4, 5]. GE contribution to the glucose disposal is reduced about to 50% after an OGTT and 30% at the end of the euglycemic hyperinsulinemic clamp (EHC) [17]. GE contributes significantly to the efficient disposition of glucose also under conditions of reduced insulin action and prevailing hyperglycemia [5]. Therefore, GE is an independent risk factor for the development of T2D in individuals with a family history of T2D [18] and obese children [15]. Weiss et al. validated a surrogate of GE, derived from the OGTT ($_{O}$GE), against GE estimated by an intravenous glucose tolerance test (IVGTT), in the pediatric obese population of the Yale study cohort [15], finding it predictive of T2D risk. In the Yale cohort, the correlation between oGE and $_{IVTT}$GE was 0.51 in NGT cases.

Since prediabetes and T2D are more prevalent in patients with clustering metabolic abnormalities [19, 20] and in those with non-alcoholic fatty liver disease (NAFLD) [20, 21], we speculated that GE was reduced in the latter two groups of patients as compared to obese peers free of any metabolic abnormality.

The aim of the present study was to investigate whether obese young patients with metabolic abnormalities and/or suspected NAFLD have reduced $_{O}$GE as compared to age, sex and body mass index matched peers with no metabolic abnormality.

Methods

Patients

Data of patients newly referred to the Units of Clinical Nutrition or Endocrinology at the Bambino Gesù Children's Hospital between 2012 and 2015 by general practitioners for overweight or obesity were revised for the purposes of the present study.

Inclusion criteria for patients' data entry were the following: Caucasian race, age 6.0–17.9 years old, complete dataset including anthropometrics body weight and height, clinical (blood pressure) and laboratory parameters (5 points OGTT with estimation of glucose and insulin at each timepoint, lipid profile) all collected and annotated according to a standardized research protocol [22].

Whenever available, values of uric acid, alanine- (ALT) and aspartate-amino transferases (AST) were annotated. Exclusion criteria were secondary obesity, chronic diseases, malformations, recent (in the previous 6 months) lifestyle, drug or weight losing treatment.

The study protocol 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. Personal and clinical data of patients were rendered anonymous before 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 data storage and handling to ensure patient data protection and confidentiality.

Anthropometrics and clinical evaluation

Weight was measured with scales certified for medical use (90/384/EEC, SECA, Hamburg, Germany) with a precision of 50 g with children wearing minimal clothing and weight recorded to the nearest 100 g. Height was measured with a Holtain stadiometer and recorded to the nearest 0.5 cm. The average of 2 measurements was used. *Z* scores of weight, height and BMI were computed based on the Italian growth charts [23]. 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.

Systolic and diastolic blood pressure (mean of three measurements) was measured on the right arm with the participant seated in a quite office with an automated oscillatory system and appropriately sized arm cuffs (Dinamap; Criticon Incorporated, Tampa, FL).

Evaluation of insulin metabolism

A standard OGTT (1.75 g of glucose per kilogram of body weight up to a maximum of 75 g) was performed. The HOMA_IR, the HOMA of percent β-cell function (HOMA-β%) [24], the Matsuda Insulin Sensitivity Index (ISI) [25], the Hepatic Insulin Resistance Index (HIRI) [25], the Insulinogenic Index (IGI) and their product, the Oral Disposition Index (oDI), were all calculated as elsewhere described [26, 27]. The areas under the glucose and insulin curves (AUC_G and AUC_I) were computed from 0 to 30 min and from 0 to 120 min in both cases. Ratios were computed as well [26].

The oGE was estimated as described in Weiss et al. [15] who adapted to obese children parameters from adult population as described originally by Nagasaka et al. [28].

Laboratory evaluation

Fasting triglycerides (TG), HDL-cholesterol, low-density lipoprotein cholesterol, and total cholesterol levels were assessed using colorimetric kits (modular systems P/S Can 433; Roche/Hitachi). Serum ALT, AST, and uric acid were assayed using a radioimmunoassay method (ADVIA 1650; Bayer Diagnostics). Blood glucose level was measured by the glucose oxidase technique (Cobas Integra; Roche), and insulin by a chemiluminescent immunoassay method (ADVIA Centaur analyzer; Bayer Diagnostics).

Case definition

Overweight was defined as BMI z score ≥ 1.036 SDS and obesity as BMI z score ≥ 1.645 SDS. IFG (fasting glucose ≥ 100 mg/dl), IGT (2 h glucose ≥ 140 mg/dl) and T2D (fasting glucose ≥ 126 mg/dl or 2 h glucose ≥ 200 mg/dl) were diagnosed according to the ADA criteria [29]. NAFLD was suspected based on the National Health and Nutrition Examination Survey-derived thresholds of ALT levels (25.8 U/L in boys and 22.1 U/L in girls) [30].

Metabolic risk parameters were considered low HDL-cholesterol as HDL ≤ 10th percentile and high fasting glucose (G0), total cholesterol, TG, and high blood pressure (either systolic or diastolic) whenever ≥ 90th percentile for age and sex in the studied population. A MetS score was computed as described by Martino et al. [31] as the sum of all the above metabolic abnormalities (0 if absent, 1 present). Therefore, the total metabolic score could range from 0 to 6. The sample was then stratified according to the Met score and patients with score 0 were considered at low risk, with 1 and 2 at medium risk and ≥ 3 at high risk.

Statistical analysis

Continuous variables were all not normally distributed. Therefore, data were reported as median and inter quartile-range (IQR) and non-parametric based-ranks tests were used to evaluate significant differences between groups. Inter-groups comparisons were carried out using the Wilcoxon or the Kruskal–Wallis tests while the measure of correlation between two quantitative variables were estimated by the Spearman correlation test. The following age-classes were identified: 6–8 (N = 95); 8–10 (N = 182); 10–12 (N = 243); 12–14 (N = 292); 14–16 (N = 140); and > 16 years of age (N = 60). A p value at 5% was considered to be statistically significant. Statistical analysis was carried out using the software R.

Results

Study population and distribution of metabolic abnormalities

The study population included 1012 patients with complete dataset; 501 (49.51%) were males and 511 (50.49%) females: 74 (7.31%) overweight and 938 obese (92.69%).

Thirty-two patients (3.16%) had IFG; 120 (11.86%) IGT and two patients (0.2%) overt T2D. One hundred and fifteen patients (11.36%) were classified as having low-HDL, 121 (11.96%) high fasting glucose, 110 (10.87%) high TG, 110 (10.87%) high total cholesterol, 181 (17.86%) high diastolic blood pressure and 138 (13.64%) high systolic blood pressure.

Four hundred and eighty-three patients (47.73%) were without any risk factor, 327 (32.31%) with one factor, 161 (15.91%) with two, 38 (3.75%) with three and 3 (0.3%) with four. Accordingly, once categorized based on the MetS score, the 483 patients (47.73%) free of any risk factor were considered at low metabolic risk, 488 at medium risk (48.22% with 1 or 2 risk factors) and 41 (4.05%) at high risk for the metabolic syndrome having 3 or more risk factors. Table 1 reports anthropometrics and metabolic characteristics of the whole sample and patients belonging to each risk category.

In 537 patients, liver function tests were assayed and 250 of them (47.86%) had serum concentration of ALT above the threshold, thus suggesting the occurrence of NAFLD.

Glucose effectiveness and metabolic abnormalities

Glucose effectiveness was significantly reduced in obese [3.81 (1.46) mg/dl/min^{-1}] vs. overweight [4.98 (1.66) mg/dl/min^{-1}; p value < 0.001] patients. oGE was negatively correlated with BMI ($\rho = -0.79$; $p < 0.001$), body

Table 1 Study population ($N=1012$)

	Whole sample $N=1012$ (100%)		Low risk (0) $N=483$ (47.73%)		Medium risk (1–2) $N=488$ (48.22%)		High risk (>=3) $N=41$ (4.05%)		*p value*
Age (years)	11.92	3.86	11.86	3.78	11.92	3.99	12.07	2.3	0.869
Weight (kg)	70.45	27.82	68	25.5	71	30.06	77.3	25.2	0.003
Height (cm)	153	19.23	153	18.95	152.35	21	157	13	0.092
BMI (kg/m^2)	29.69	5.7	29.21	4.97	30.1	6.27	30.7	6.82	<0.001
BMI *z* score (sds)	2.34	0.69	2.26	0.67	2.37	0.69	2.61	0.74	<0.001
HDL (mg/dl)	45	13	47	11	43	13	37	14	<0.001
Tot. cholesterol (mg/dl)	155	37	150	30.5	159	44	170	49	<0.001
Triglycerides (mg/dl)	80	53.25	72	35.5	89	70.25	174	110	<0.001
AST (µUI/ml)	25	9	24	8	26	9.25	27.5	9.25	0.019
ALT (µUI/ml)	23	13	21.5	11	24	14	28	25.25	<0.001
Fasting glucose (mg/dl)	83	10	82	8	84	13	87	15	<0.001
2 h Glucose (G_{120} mg/dl)	112	26	109	24	114	29	121	33	<0.001
Fasting insulin (I_0 µUI/ml)	16.89	13.8	15.2	10.8	17.7	13.96	32.8	25.5	<0.001
HOMA-IR	3.48	2.77	3.05	2.29	3.73	3.02	6.4	5.5	<0.001
Matsuda index (µmol kg^{-1} pM)	3.32	2.16	3.08	2.26	2.41	1.82	1.66	0.82	<0.001
Insulinogenic index (µIU/ml × mg/ml^{-1})	36	37.17	33.89	35.94	37.3	39.31	52.8	44.65	0.030
$_{O}$DI	100	90	107.58	97.31	92.28	84.43	82.79	101.3	0.006
Hepatic insulin resistance index (mmol/l × min^{-1})	6.53	6.66	5.29	5.88	7.51	6.79	9.41	11.11	<0.001
AUC_{G0-30}/AUC_{I0-30}	1.65	1.69	1.97	1.87	1.49	1.5	1.34	1.24	<0.001
$AUC_{G0-120}/AUC_{I0-120}$	1.19	0.96	1.29	1.02	1.16	0.89	0.86	0.56	<0.001
oGE (mg/dl/min^{-1})	3.88	1.54	4.03	1.46	3.74	1.67	3.48	1.09	0.001

Data are expressed as median and interquartile range

P refers to the statistical significance at the Kruskal–Wallis test between risk levels

BMI body mass index, *HDL* high-density lipoprotein cholesterol, *AST* aspartate amino transferases, *ALT* alanine aminotransferases, *HOMA* Homeostasis model assessment, *oDI* oral disposition index, *oGE* OGTT-derived glucose effectiveness, *AUC* area under the curve

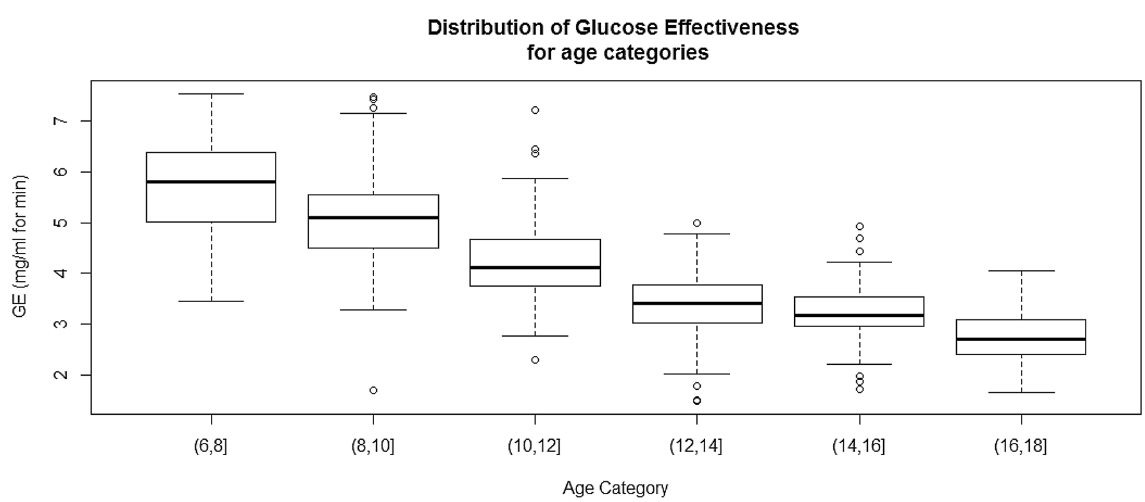

Fig. 1 Boxplot of Glucose Effectiveness distribution for patients divided in age categories

weight ($\rho = -0.96$; $p < 0.001$) and BMI-z score ($\rho = -0.56$; $p < 0.001$).

Median values of oGE were significantly different among age categories ($p < 0.001$) showing a decline from early to late childhood (Fig. 1). Indeed, oGE was inversely correlated with age ($\rho = -0.77$; $p < 0.001$). No difference between sexes was found in oGE.

oGE was significantly reduced in patients with high systolic [3.65 (1.25) vs. 3.89 (1.55) mg/dl/min^{-1}, p value = 0.04] and diastolic blood pressure [3.68 (1.21) vs. 3.99 (1.61) mg/dl/min^{-1}, p value < 0.001] and correlated with values of systolic ($\rho = -0.43$; $p < 0.001$) and diastolic blood pressure ($\rho = -0.24$; $p < 0.001$). oGE was also significantly related with triglycerides ($\rho = -0.17$; $p < 0.001$), HDL cholesterol ($\rho = 0.30$; $p < 0.001$) and total cholesterol ($\rho = -0.13$; $p < 0.001$).

oGE decreased significantly among MetS risk classes and differences were outlined statistically significant among low, medium and high-risk levels ($p = 0.001$). The higher the oGE, the smaller the MetS score (Fig. 2). The median percentage difference of oGE from low to medium risk was estimated to be as −4.9%, but from medium to high risk as −13.38% and from low to high risk as −17.62%.

Finally, there was a positive correlation between oDI and oGE ($\rho = 0.29$; $p < 0.001$).

Glucose effectiveness and metabolic risk score in NAFLD+ cases

In a subsample of patients with no missing data on liver function tests [$N = 537$, 247 males (46%) and 290 females (54%); 38 (7.08%) overweight and 499 obese (92.92%)], oGE was not statistically different between cases with suspected NAFLD vs. cases without [NAFLD+ $N = 250$, 3.82 (1.75) vs. NAFLD− $N = 287$, 3.9 (1.55) mg/dl/min^{-1}, $p = 0.1$].

In NAFLD+ cases [4.48 (3.66)], HOMA-IR was higher than in NAFLD− cases [3.48 (2.51); $p < 0.001$] as well as the hepatic insulin resistance index [NAFLD+: 8.87 (8.31) vs NAFLD−: 6.69 (6.25); $p = 0.001$]. The Matsuda [NAFLD+: 1.99 (1.32) vs. NAFLD− 2.77 (1.99) μmol·kg-1·pM^{-1}; $p < 0.001$] and the QUICKI index [NAFLD+: 0.033 (0.04) vs. NAFLD− 0.31 (0.04), $p < 0.001$] were both significantly reduced in NAFLD+ cases. No significant differences were found in the IGI and the oDI.

The distribution of the MetS risk score was statistically ($p < 0.001$) different in NAFLD+ vs. NAFLD− cases. MetS risk score was distributed as it follows: in NAFLD+ ($N = 250$), 105 (42%) were at low risk, 136 (54.4%) at medium and nine (3.6%) at high risk; in NAFLD− cases ($N = 287$) 161 (56.1%) were at low, 119 (41.46%) at medium and seven (2.44%) at high risk.

Discussion

The results of the present study demonstrate that oGE is reduced not just in relation to the obesity condition but independently of the higher BMI, in those who carry metabolic abnormalities. Obese patients with high metabolic risk score had 17.62% reduced oral glucose effectiveness respect with obese patients with low metabolic risk score.

It is well known that the clustering of metabolic abnormalities under the umbrella of the metabolic syndrome enhances the individual's risk of developing T2D [20, 21]. Our findings suggest that glucose effectiveness decreases in parallel with the overall progression of metabolic derangement that accompanies the obesity status and that impaired oGE may contribute to the development of impaired glucose

Fig. 2 Glucose effectiveness distribution for MS risk levels

tolerance. Such contribution seems not depending on the degree of insulin action, secretion or their hyperbolic relationship, the latter exactly representing the oDI.

Weiss et al. [15] demonstrated that reduced oGE predicts significantly young subjects converting from normal glucose tolerance (NGT) to IGT along with the baseline 120 min glucose level. Indeed, in the Yale series of young obese patients, low oGE predicted incident IGT and T2D in a way that was not dependant upon the oral disposition index. Both reduced oDI and oGE values were independently and synergistically associated with higher 2 h glucose levels on the OGTT results. In our series, there was a positive correlation between oGE and oDI. Weiss et al. found NGT individuals having significantly higher oGE than obese patients with IFG and IGT. Among age, sex, ethnicity, weight category, glucose tolerance and oDI, the degree of obesity remained the main significant predictor of oGE. Along with the Weiss' study, Hoffman et al. investigated the GE of seven prepubertal obese patients as compared with six lean subjects using the IVGTT. They found the obese patients having significantly higher GE than lean peers. Both hepatic and systemic insulin resistance as well as early insulin secretion were significantly increased. The Authors postulated that the increase of GE was to compensate for the insulin resistance [8].

The route of the glucose challenge may contribute to explain such divergences. Indeed, oral glucose is taken up from intestinal lumen trough the Na^+/glucose cotransporter (SGLT1) and the glucose transporter type 2 (GLUT2) into enterocytes where it is metabolized in part and independently of the insulin [32]. The binding to SGLT1 seems to influence the release of gastrointestinal hormones that modulate insulin secretion [33], thereby affecting oDI.

In patients with suspected NAFLD, median oGE was not statistically different from values found in obese patients without fatty liver despite NAFLD+ cases had enhanced hepatic insulin resistance (higher HOMA-IR) and reduced whole-body insulin sensitivity. The liver is crucial for the maintenance of normal glucose homeostasis [34]. Net hepatic glucose production (HGP) is the summation of glucose fluxes from both gluconeogenesis and glycogenolysis and both components of HGP are regulated by glucose per se coupled with insulin action. In adult patients with biopsy-proved NAFLD, Bugianesi et al. [34] did not observe any relationship between post-absorptive (insulin-independent) or insulin-suppressed HGP and the percentage of hepatic fat during a two-step euglycaemic insulin clamp coupled with tracer infusion ([6,6-2H2]glucose and [2H5]glycerol).

Finally, the finding that oGE decreases significantly from early to late childhood and adolescence across age categories would be of great interest if confirmed by future studies.

Despite the concept of GE was described in the late 70 s, it has been underappreciated for a long time and it still remains a little understood factor in the regulation of glucose tolerance, the importance of which deserves to be increasingly appreciated. The ability of glucose to promote its own disposition by way of enhancing glucose uptake and suppressing glucose production plays a major role in glucose disposal during fasting, yet it has a significant effect on post-absorptive glucose uptake as well. The major limitation to wide studies of GE in adults and even more in children and adolescents is the need to use cumbersome techniques to estimate it (i.e. clamping or IVGTT). The validation of the oGE formula in the pediatric population, conversely, might favor the spreading of such estimate as it has been for OGTT-derived estimates of insulin sensitivity leading to the better understanding of the T2D pathogenesis in young age. Such validation can profoundly impact on the phenotyping of young obese patients and this novel surrogate, in combination with other clinical and metabolic parameters, may help to identify obese children and adolescents who are at risk for diabetes.

Nevertheless, we believe the accuracy of this formula as developed by Nagasaka et al. [28] may need further validation in larger and different populations and, perhaps, improvement. Glucose effectiveness is intrinsically a "difficult" parameter to be assessed, even from the IVGTT and the clamp. The situation may get even more problematic when the estimation is performed by the OGTT. For instance, the formula is based on a couple of assumptions such as the fixed absorption rate of glucose and the hyperbolic relationship between insulin sensitivity and secretion, while these assumptions are not always true. In youngsters from the Yale cohort, the formula worked better in subjects with NGT than in those with altered glucose tolerance, but in both cases, the correlation was weak despite being highly statistically significant (15). Nevertheless, reduced oGE predicted T2D. Nevertheless, this index may be helpful to identify young individuals at metabolic risk.

We are aware of other caveats affecting the present study, i.e. cross-sectional design, lack of normal weight controls and information on pubertal stage, use of a metabolic score to overcome the issue of defining the metabolic syndrome in children below age 10, use of ALT to identify individuals at risk of NAFLD. Longitudinal evaluation of large populations are needed to verify whether reduced oGE of obese children carrying metabolic abnormalities increases significantly the risk of T2D and how oGE changes at puberty.

Conclusions

Glucose effectiveness is reduced in obese young patients with metabolic abnormalities independently of adiposity as compared to obese peers with no abnormality and may contribute to explain their higher risk to develop T2D.

Funding There was no fund supporting the study.

Compliance with ethical standards

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

Ethical approval All procedures performed in the study were in accordance with the ethical standards of the Ethics Committee of Bambino Gesù Children's Hospital, which approved the study, and with the 1964 Helsinki Declaration and the European Convention of Human Rights and Biomedicine for Research in Children as revised in 2008. To ensure data protection and confidentiality, data extracted from the medical records were de-identified before analysis.

Informed consent Written informed consent was obtained from the parents before any testing procedure.

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