EVALUATING INSULIN RESISTANCE IN CHILDREN: A CRITICAL APPRAISAL OF MINIMAL MODELS

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ABSTRACT

Childhood obesity has followed, during the last two decades, an ascending trend. Insulin resistance (IR) is central to the pathophysiology of obesity. So far, several methods of assessing IR have been proposed.
We aimed to evaluate critically some of the simplest methods used to assess IR in the pediatric population. We studied retrospectively the records of children evaluated for obesity in the "Louis Țurcanu" Emergency Hospital for Children Timişoara, over a period of 10 years. The study population consisted of 342 children. Anthropometric and metabolic variables were analyzed, and the following indices of IR were assessed: impaired glucose tolerance (IGT), Homeostatic Model of Assesment-IR (HOMA-IR), Homeostatic Model of Assesment- b (HOMA-β), Quantitative Insulin Sensitivity Check Index (QUICKI) as well as the TG/HDLc ratio. Data was expresed as frequencies, means ± standard deviations or median ± interquartile interval for or a 95% confidence interval. The t-test for independent groups or the Mann-Whitney test to assess differences of IR indices across weight, gender and pubertal categories.
HOMA-IR diagnosed the most children with IR, at the opposite pole we found QUICKI. IGT was a rare finding. It is necessary to reconsider how we assess the carbohydrate metabolism in children. Of the methods we evaluated, HOMA-IR is the optimal method for assessing IR children.

Keywords: Homeostatic Model, oral glucose tolerance test, Quantitative Insulin Sensitivity Check Index, insulin resistance, insulin sensitivity, impaired glucose tolerance, children.

Abbreviations:

BMI – body mass index,
HDL – high density lipoproteins,
HDLc – high density lipoproteins cholesterol,
HOMA-β – Homeostatic Model of Assesment- β,
HOMA-IR – Homeostatic Model of Assesment-IR,
IGT – impaired glucose tolerance,
IR – Insulin resistance,

IR+ – insulin resistant children,
IR- – insulin sensitive children,
QUICKI – Quantitative Insulin Sensitivity Check Index,
SD – standard deviation,
TG – triglycerides.
OGTT – oral glucose tolerance test

INTRODUCTION

Childhood obesity has followed, during the last two decades, an ascending trend, visible in all population groups, at global, regional and national levels (14). Insulin resistance (IR) and hyperinsulinemia are central to the pathophysiology of obesity, and will cause abnormalities of carbohydrate and lipid metabolism, as well as hypertension (13,20,21,25). So far, several methods of assessing IR have been proposed (4,6,8,20,21,23,27). Of these, most are laborious, expensive; require special equipment and multiple blood samples, last long, being accessible only to certain specialized centers. On the other hand, some are obtained using different formulas from glucose, insulin or lipids' values. Furthermore, standards defining IR in the pediatric population are lacking (6,8,17,23). The

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aim of the present study was to evaluate critically some of the simplest methods used to assess IR in the pediatric population.

MATERIAL AND METHODS

We performed a retrospective analysis of 475 records of children evaluated for obesity in the "Louis Țurcanu" Emergency Hospital for Children, Timisoara. The review period was: January 2000 - December 2010.

We included children aged 5 to 18.5 years at the time of enrollment and a body mass index (BMI) above the 85th percentile for age and sex (World Health Organization (WHO) growth standards). Exclusion criteria were: birth weight less than 2800 grams and above 4200 grams, a gestational below 38 weeks and above 42 weeks, a height less than -1DS for age and sex, clinical signs of infectious diseases, syndromes associated with obesity, treatments affecting blood pressure, carbohydrate and lipid metabolism. The study population consisted of 342 children.

We analyzed the following variables: age, sex, weight, height, for which BMI (weight divided by the square of height) and its standard deviation score was calculated, baseline, and 2 hours glucose derived from the oral glucose tolerance test (OGTT, (1.75 g of glucose per kilogram of body weight; maximal dose, 75 g)), triglycerides (TG), high density lipoproteins fraction of cholesterol (HDLc), baseline insulin.

The following indices of IR were assesed: impaired glucose tolerance (IGT), Homeostatic Model of Assesment-IR (HOMA-IR= baseline insuline X baseline glucose/22.5), Homeostatic Model of Assesment-b% (HOMA- b% = 20 X baseline insulin / (baseline glucose-3.5)), and Quantitative Insulin Sensitivity Check Index (QUICKI= 1/(log (baseline insulin) + log (baseline glucose))), TG / HDLc ratio.

IGT was established when the 2 hours glucose value was above 7.8 mmol/l, but less than 11.1 mmol/l. HOMA-IR, HOMA- b% and QUICKI were interpreted using specific values for sex and pubertal stage (Table 1). For the TG/HDLc ratio a normal value of less than 2.5 was considered.

Depending on the threshold values of the indices we divided the children into two groups: children with IR (IR+), and insulin-sensitive children (IR-), respectively. Using the WHO growth standards we cathegorized children as overweight (BMI above the 85th percentile for age and sex, but below the 97th) or obese (BMI above the 97th percentile for age and sex). We considered the age 10 as the threshold between prebupertal and pubertal children.

STATISTICAL ANALYSIS

Data were expressed as frequencies, means ± standard deviations or median ± interquartile range, as appropriate. The t-test for independent groups and the Mann-Whitney test, respectively, was used to assess differences of IR indices across weight, gender and pubertal categories (confidence interval 95%). The analysis was performed using SPSS.

RESULTS

Descriptive characteristics of the study population are presented in Table 2.

We found that 50% of the children had IR, when using HOMA-IR. In our population, 8.79% of the children had IGT (Fig. 1 and 2). IR indices across weight, gender and pubertal categories are presented in Table 3.

DISCUSSION

The results suggest the need to reconsider how we assess the carbohydrate metabolism in children

TABLE 1. *Cut-off values corresponding to the 90th and 95th percentile, according to gender and pubertal status for IR indices*

		Girls		Boys	
		90th percentile	95th percentile	90th percentile	95th percentile
HOMA-IR	Prepubertal	2.12	2.2	2.11	2.2
	Pubertal	3.64	4.36	2.47	2.72
HOMA-b%	Prepubertal	184.7	192.1	133.3	154.7
	Pubertal	421.8	487.4	249.1	363.4
QUICKI	Prepubertal	0.42	0.43	0.44	0.45
	Pubertal	0.39	0.45	0.41	0.42

HOMA-IR denotes Homeostatic Model Of Assessment-Insulin resistance; HOMA-b%, Homeostatic Model Of Assessment-b%; QUICKI, Quantitative Insulin Sensitivity Check Index; for HOMA-IR and HOMA- β the IR status is established if the value is above the cut-off; for QUICKI the IR status is established if the value is below the cut-off. Modified after d'Annunzio et al (11).

TABLE 2. *Descriptive characteristics of the study population*

	N	Min.	Max.	Mean Median	SD/ Interquartile range	Skewness	Kurtosis
Age	342	5.0	18.4	11.907	2.9663	.033	-.600
Weight	342	25.50	130.00	67.4336	22.37665	.384	-.559
Height	342	114.0	197.0	154.076	14.7366	-.299	-.040
BMI	342	17.53	49.09	27.5922	5.49736	.790	.551
BMI z score	342	1.00	4.94	2.6287	.77077	.437	.464
Baseline glucose	292	2.50	6.96	4.7200	.70	-.119	2.426
2 hours glucose	239	2.72	10.20	6.0133	1.30904	.416	.441
Triglycerides	263	.33	4.53	1.0900	.73	1.925	6.266
HDL cholesterol	115	.26	4.50	1.2000	.37	3.055	11.984
Baseline insulin	152	2.00	87.90	12.300	10.38	3.066	18.408
HOMA-IR	146	.38	18.48	2.79	2.74	2.891	15.592
HOMA-b%	146	-7742.86	1429.27	242.215	222.2	-9.524	103.785
QUICKI	146	.38	1.07	0.56	.12	1.620	4.915
TG/HDLc	113	.15	9.65	1.07	0.82	3.836	17.623

BMI, denotes Body Mass Index; z score standard deviation score; SD, standard deviation; HDL, high density lipoproteins; HOMA-IR, Homeostatic Model Of Assessment-Insulin resistance; HOMA-β, Homeostatic Model Of Assessment- β; QUICKI, Quantitative Insulin Sensitivity Check Index; TG, triglycerides; HDLc, high density lipoproteins cholesterol.
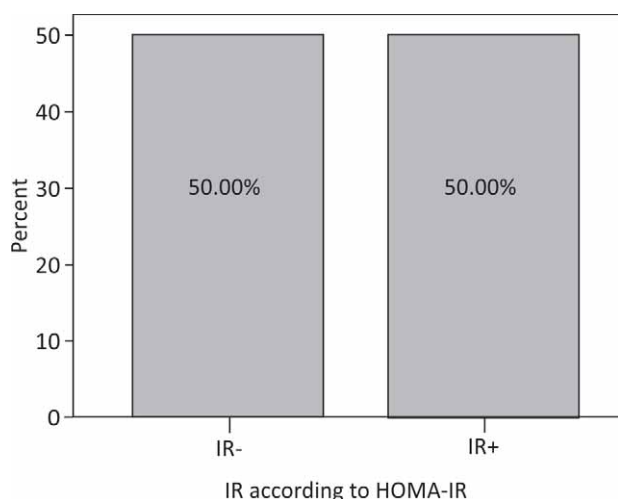

FIGURE 1. *Insulin resistance according to HOMA-IR.*
HOMA-IR denotes Homeostatic Model Of Assessment-Insulin resistance; IR+, insulin resistant children; IR-, insulin sensitive children.

and the thresholds defining its various anomalies. Of the methods we have evaluated, HOMA-IR is the optimal method for assessing the IR status in overweight and obese children.

HOMA-IR diagnosed by far the most children with IR. In the international community, several studies found that HOMA-IR is an excellent tool for assessing IR in children (2, 11, 26, 28). Furthermore, the method is simple and easy to use in practice, only a single blood sample being required for its calculation.

HOMA-IR vs. OGTT

Currently, OGTT is widely used to assess glucose metabolism anomalies in children.

IGT was rare in our study, and there were no significant differences between overweight and obese children, between gender and pubertal categories.

Similar studies found higher rates of IGT in the obese population: 12-25% (8, 22, 24). The low frequency found by us is due to the fact that we excluded children with major abnormalities of glucose metabolism, including in our analysis overweight children as well.

TABLE 3. *IR indices across weight, gender and pubertal categories*

	Overweight Mean ± SD	Obese Mean ± SD	p	Boys Mean ± SD	Girls Mean ± SD	p	Prepubertal Mean ± SD	Pubertal Mean ± SD	p
HOMA-IR	2.35 ± 1.42	3.26 ± 2.25	0.083	3.09 ± 2.42	3.28 ± 1.90	0.338	2.77 ± 1.73	3.28 ± 2.29	0.262
OGTT	6.51 ± 1.49	5.94 ± 1.27	0.034*	6.09 ± 1.38	5.90 ± 1.20	0.247*	5.92 ± 1.18	6.03 ± 1.34	0.567*
HOMA-b%	216.99 ± 192.9	191.53 ± 752.6	0.126	204.96 ± 340.96	179.89 ± 1014.7	0.006	267.72 ±181.43	175.48 ±799.28	0.801
QUICKI	.60 ± .07	.57 ± .10	0.085	.58 ± .09	.57 ±.11	0.388	.59 ± .09	.57 ± .10	0.229
TG/HDLc	1.24 ± .72	1.40 ± 1.50	0.797	1.45 ± 1.48	1.31 ± 1.41	0.476	.96 ± .54	1.46 ± 1.55	0.182

SD denotes standard deviation; HOMA-IR Homeostatic Model Of Assessment-Insulin resistance; HOMA-β, Homeostatic Model Of Assessment- β; QUICKI, Quantitative Insulin Sensitivity Check Index; TG, triglycerides; HDLc, high density lipoproteins cholesterol; * the statistical significance of the t-test; p denotes the statistical significance of the Mann-Whitney test.
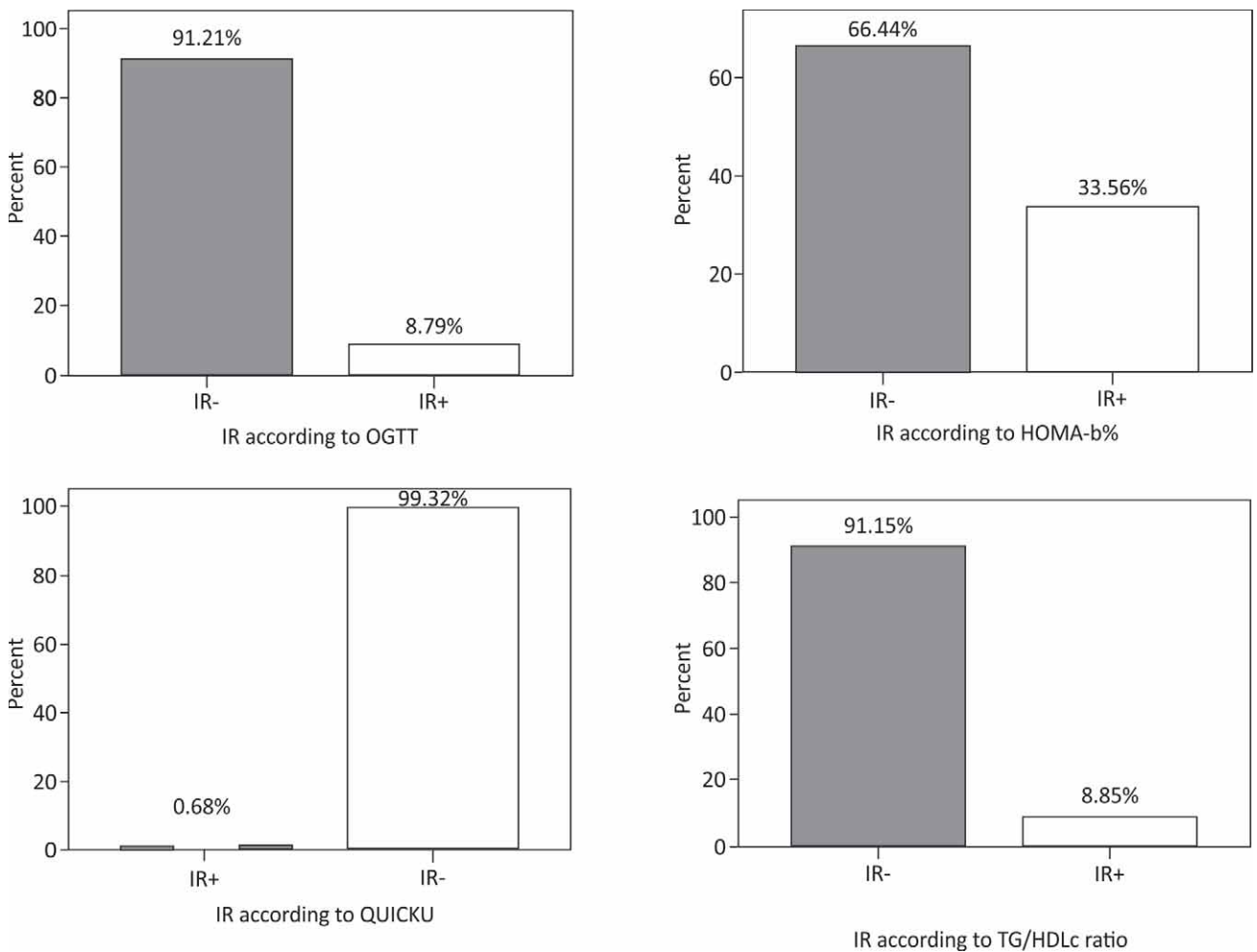
FIGURE 2. Impaired glucose tolerance (A, up, left), HOMA-b% (B, up, right), QUICKI (C, down, left) and TG/HLc ratio (D, down, right).
OGTT denotes Oral Glucose Tolerance Test; HOMA-b%, Homeostatic Model Of Assessment-b%; QUICKI, Quantitative Insulin Sensitivity Check Index; TG, triglycerides; HDLc, high density lipoproteins cholesterol; IR+, insulin resistant children; IR-, insulin sensitive children.

It is considered that glucose tolerance and insulin sensitivity are not equivalent terms, thus OGTT provides information about glucose tolerance and not specifically about IR (29). In addition, the OGTT has poor reproducibility in practice, children with discordant values at 2 separate OGTTs are more IR and have a worse metabolic profile (24). Using only the baseline glucose value, glucose metabolism abnormalities remain unidentified in 70% of cases (24). Even more worrisome is that the results of the Bogalusa Heart Study (31) show that elevated but normal basal blood glucose are associated with diabetes 2 in adulthood.

Because IGT was rare in our study, and IR assessed by HOMA-IR frequent, we believe that evaluating glucose metabolism using OGTT, delays finding its abnormalities. Furthermore, this leads to delaying of early interventions aimed at changing lifestyle and achieving and maintaining optimal weight.

In children, it has been shown that early interventions are associated with reducing metabolic risk (7, 28, 30). In addition, interventions aimed at younger children are most effective (34).

HOMA-IR vs. QUICKI

QUICKI found the least children with IR. Both HOMA-IR, and QUICKI are considered precise, reproducible and reliable indices (29). It seems that QUICKI appreciates IR better in extreme cases: very high blood glucose or very small insulin values, while HOMA-IR does not provide an accurate assessment when β-pancreatic function is profoundly altered (29). We excluded children with major alterations in carbohydrate metabolism from our study population, thus we believe that IR status is accurately appreciated by the two indices.

HOMA-IR vs. HOMA- b %

In our study, HOMA- b % ranked second after HOMA-IR as a method of assessing the status of IR. HOMA-b % was designed with HOMA-IR, and

is useful for assessing β-pancreatic function (29). We emphasize once again that in our group were excluded children with significant changes of the β pancreatic function, so the IR status of our children as determined by HOMA-b % is accurate.

HOMA-IR vs. TG/HDLc

Although various studies have demonstrated the usefulness of including TG and HDLc in different formulas that assess IR (1, 16, 19), the TG/HDLc ratio identified only a small percentage of children with IR. This finding may be due to the fact that we used a single threshold for defining IR when using the TG/HDLc ratio. This could be a problem because TG and HDLc values vary with age, gender and pubertal stage (12). Further studies are needed to address these issues.

CONCLUSIONS

It is necessary to reconsider how we assess the carbohydrate metabolism in children and the thresholds defining its various anomalies. Of the methods we evaluated, HOMA-IR is the optimal method for assessing the IR status in overweight and obese children. The OGTT delays the finding of glucose metabolism abnormalities in children. QUICKI and HOMA-b% are poor indices of IR when no major anomalies of carbohydrate metabolism are present. Further studies are needed to evaluate the use of TG and HDLc in defining IR. I

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