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Hyperinsulinism assessment in a sample of prepubescent children

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Abstract

Objectives: To determine the relationship between body mass index (BMI), homeostasis model assessment – insulin resistance (HOMA-IR) and insulinemia.

Methods: This was a prospective cross-sectional observational study of 132 prepubescent schoolchildren residents in the municipality of Santo André, Brazil. Children underwent anthropometric assessment, their glycemia and insulinemia were measured and their HOMA-IR index calculated.

Results: Seventy-eight of the 132 children (59.1%) were girls and 54 were boys (40.9%), with a mean age of 8.7 years and mean BMI of 13.7 kg/m^2. A significant positive association was detected between HOMA-IR and BMI, insulin and BMI, weight and HOMA and between insulin and weight. It was also found that the higher the BMI, the greater the HOMA score.

Conclusions: The results of this study allow for the conclusion that there is a strong association between hyperinsulinism and obesity. Measures should be taken to avoid weight gain during childhood and adolescence.

J Pediatr (Rio J). 2010;86(3):245-249: Blood samples, hyperinsulinism, glucose.

Introduction

Insulin is a hormone secreted by the pancreas, stimulated by amino acids, fatty acids (FA), ketone bodies and especially glucose. The secretion process is strongly regulated to maintain stable blood glucose levels in both fasting and postprandial conditions.[1] Insulin also regulates the activity of some enzymes involved in FA synthesis: it counterbalances the effects of epinephrine, reducing the activity of triacylglycerol lipase and consequently the hydrolysis of triacylglycerols (TG) (stored in adipose tissue) for the release of free FA.[2]

Insulin promotes the use of glucose for energy production and stimulates storage of glucose excess as fat.[2,3] Thus,

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hyperinsulinism may signal the development of several metabolic disorders[4] associated with cardiovascular disease (CVD).

Insulin resistance (IR) is defined as a state of subnormal biological response to serum insulin levels,[5,6] and is frequently associated with hyperinsulinism in an attempt to obtain an adequate physiological response.[4,6,7] One of the indicators used for IR assessment is the homeostasis model assessment – insulin resistance index (HOMA-IR).[8] This index has been widely used because it is a fast, easy and low-cost method,[6] and it has been recommended even for pediatric age groups.[8] Moreover, it provides an indirect IR measurement[6,9] through the assessment of endogenous insulin and glycemia in homeostasis and fasting conditions. HOMA-IR has been used in studies with large populations,[6] because it only requires one fasting sample to assess glycemia and insulinemia.[10] The following equation is used to calculate the index: fasting insulinemia (FI, in µUI/mL) x fasting glycemia (FG, in mmol/L)/22.5[11]. When first described, the HOMA-IR index was adjusted so that a 35-year old healthy individual would present a result equal to 1.[12]

The prevalence of obesity in children is an endemic problem,[1] although some authors have argued that the it has already reached epidemic levels.[4,13] Estimates have suggested that the prevalence of obesity will reach 5% of the pediatric population worldwide by 2010.[14] A study conducted in some Brazilian cities revealed that overweight and obesity affect more than 20% of children and adolescents.[15] Data from the Brazilian National Demographic and Health Survey (Pesquisa Nacional de Demografia e Saúde) indicate a prevalence of 7% of overweight in children under 5 years of age.[16]

Obesity increases the risk for development of CVD and affects the patient's physical and social functioning and quality of life.[13] The presence of obesity during childhood and adolescence acts as an important risk factor for its persistence and for the development of CVD in adult life.[4]

FI levels are believed to vary significantly during childhood and adolescence, even under normal conditions.[13] Cuartero et al.[17] have reported the distribution of HOMA-IR percentile values for children and adolescents according to pubertal stage. In that study, the 90th percentile for prepubertal children was 1.67 for boys and 1.94 for girls.

Vasques el al.[6] have presented cutoff points for the HOMA-IR index in several populations and age groups: for Brazilian patients under 18 years of age, the cutoff point was 2.39±1.93.

Based on the above, the objective of the present study was to determine the relationship between body mass index (BMI), HOMA-IR, and insulinemia, in an attempt to prevent the development of some diseases related to hyperinsulinism and obesity in children.

Methods

This was an observational cross-sectional study of 132 prepubescent schoolchildren (66 obese and 66 at healthy weights) from a municipal school in the municipality of Santo André, SP, Brazil. The study was approved by Human Research Ethics Committee at the Faculdade de Medicina do ABC (FMABC) in Santo André.

The initial sample selection was based on the nutritional status of all children enrolled at the school: 978/1,018 (96%). Those children who were found to be obese, 146/978 (15%), were matched for age and sex with healthy children from the same classroom and invited to provide samples for laboratory tests.

On the basis of the inclusion criteria (on the roll of the school being studied; aged under 10 years and 11 months; resident of Santo André; free from chronic diseases; and with permission granted by parents or guardians) and the exclusion criteria (pubertal development; chronic diseases; parents' disagreement; or failure to attend after three invitations), a total of 66 obese patients and 66 healthy controls were enrolled.

Anthropometric assessment consisted of taking weight and height measurements as directed by the World Health Organization. Body mass index was then calculated and converted to a z score and children were defined as obese if their BMI z score was greater than +2.[6,9,16-18]

Puberty was staged according to criteria described by Marshall & Tanner.[19]

Glycemia (mg/dL) and insulinemia (µUI/mL) were assayed and the HOMA-IR index calculated. Blood samples were collected into dry tubes (to allow coagulation). A total of 10 mL of blood was taken from each child.

The samples were transported to the Clinical Analysis Laboratory at the FMABC, within a maximum of 3 hours, and centrifuged at 2,500 rpm for 10 minutes. Before this process, observations were made to ensure that coagulation was complete (in order to prevent the appearance of fibrin, since it can lead to incorrect measurements).[20]

The following criteria were used for analytical sample selection: hemolyzed samples were not analyzed (hemolysis can lead to too low results), nor were samples with bilirubin (since it can reduce figures) jaundiced samples, lipemic samples or contaminated samples.[20] Serum insulin levels were assayed using a solid-phase chemiluminescent enzyme immunoassay with two incubations (Immulite 1000, Siemens®), testing 100 µL of serum. Glycemia was assayed using the enzymatic glucose-oxidase method (Express Plus, Bayer®).

In order to calculate the HOMA-IR index, it is first necessary to convert the glycemia results expressed in mg/dL into mmol/L, which was done by multiplying them by 0.0556. The HOMA-IR index could then be calculated using the formula FI x FG/22.5.[9] The cutoff point of 2, proposed

by Cuartero et al.[17] for prepubescent children, was used for the HOMA-IR analysis.

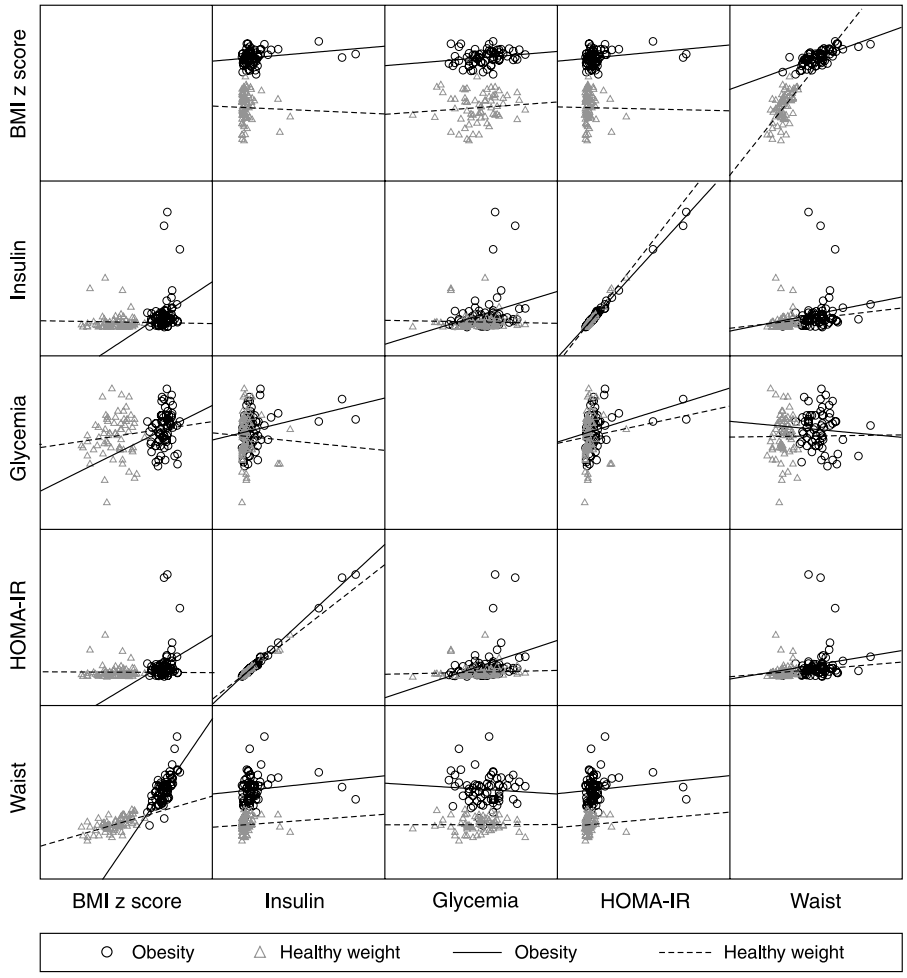
Statistical analysis employed the chi-square test to compare dichotomous and qualitative variables (sex and unhealthy HOMA-IR). Continuous variables were compared using Student's *t* test (age, BMI z score, glycemia, insulin and HOMA-IR) and correlations were analyzed using Pearson's coefficient (BMI z score against glycemia, insulin and HOMA-IR). Significance was set at $\alpha < 5\%$. However, where Pearson's coefficients were significant to $\alpha < 1\%$, this has also been indicated. Calculations were performed using SPSS 13.0.

Results

The general characteristics of the obese and healthy weight children are given in Table 1. There were more girls than boys in both groups (76/132; 59.1%), and median age was 8.7±1.1 years. Insulin resistance (HOMA-IR > 2) was observed in 24/66 (36.4%) obese children and 7/66 (10.6%) of those with healthy weight ($p < 0.001$) (data not shown).

Figure 1 illustrates the correlations between the anthropometric variables (BMI z score and abdominal waist) and the laboratory variables (glycemia, insulin and HOMA-IR). Body mass index z score had a statistically significant association with waist measurement, both among the obese children and among those with healthy weights [r obese = 0.72 ($p < 0.01$) and r healthy weight = 0.59 ($p < 0.01$)] (Table 2). In neither group was there a statistically significant correlation between BMI z score or waist measurement and insulin, glycemia and HOMA-IR.

The analysis of laboratory variables from the group of obese children showed that there was a weak correlation between insulin and glycemia ($r = 0.27$; $p < 0.05$) and a strong correlation between insulin and HOMA-IR ($r = 0.98$; $p < 0.01$). In the healthy-weight group there was only a correlation between insulin and HOMA-IR ($r = 0.98$; $p < 0.01$) (Figure 1).



BMI z score = z score for body mass index;
HOMA-IR = homeostasis model assessment – insulin resistance.

Figure 1 - Correlations between BMI z score and abdominal waist with insulin, glycemia and HOMA-IR in obese and healthy-weight children

Table 1 - Characteristics of the study population

Variable	Obese (n = 66)	Healthy weight (n = 66)	p
Sex (female/male)	37/29	41/25	0.596*
Age (years)	8.8±0.1	8.6±1.1	0.398†
Body mass index (z score)	2.1±0.3	0.6±1.0	< 0.001†
Abdominal waist (cm)	76.6±8.4	56.5±4.0	< 0.001†
Glycemia (mg/dL)	97.0±8.8	93.6±10.5	0.049†
Insulin (μU/mL)	9.7±11.5	4.9±5.1	0.002†
HOMA-IR	2.4±3.0	1.1±1.7	0.002†

HOMA-IR = homeostasis model assessment – insulin resistance.
* Significance according to chi-square test.
† Significance according to Student's *t* test.

Table 2 - Study variables for obese and healthy-weight children

	Obese children					Healthy-weight children				
	BMI z score	Waist	Insulin	Glycemia	HOMA	BMI z score	Waist	Insulin	Glycemia	HOMA
BMI z score	1	0.72*	0.24	0.20	0.23	1	0.59*	-0.03	0.10	-0.01
Waist	0.72*	1	0.14	-0.07	0.13	0.59*	1	0.09	0.00	0.07
Insulin	0.24	0.14	1	0.27†	0.98*	-0.03	0.09	1	-0.04	0.98*
Glycemia	0.20	-0.07	0.27†	1	0.32*	0.10	0.00	-0.04	1	0.07
HOMA	0.23	0.130	0.98*	0.32*	1	-0.01	0.09	0.989*	0.07	1

HOMA = homeostasis model assessment; BMI z score = z score for body mass index.
* Significance level according to Pearson's correlation coefficient: $p < 0.01$.
† Significance level according to Pearson's correlation coefficient: $p < 0.05$.

Discussion

The results of this study indicate that there is a strong association between anthropometric indices, the HOMA-IR index and insulinemia.

Almeida et al.[13] reported differences between the sexes in the 11 to 12.9 years and 15 to 17.9 years age groups, both for insulinemia and HOMA-IR [calculated using the equation FG (mmol/dL) x FI (μUI/mL)/25]. In contrast, neither Pivatto et al.[18] nor da Silva et al.[21] detected significant differences between the sexes for HOMA-IR and the first of these studies also failed to detect differences in terms of serum insulin levels. Both of these studies were with adults.

Ferreira et al.[9] indicate that insulin levels were significantly different between the sexes, being higher among girls [17.8±9.9 μUI/mL, 95% confidence interval (95%CI) 13.6-22] than among boys (11.9±5.7 μUI/mL, 95%CI 9.7-14.1). Insulin resistance figures were higher in the female sex (3.8±2.2, 95%CI 2.9-4.8) than for males (2.6±1.3, 95%CI 2.1-3.1). In contrast, HOMA-IR was elevated in obese children of both sexes. The study concluded that obese children had several risk factors for the development of cardiovascular disease and that the higher the IR, the larger number of risk factors and the greater the predisposition to emergence of metabolic syndrome, diabetes mellitus type 2 and cardiovascular diseases.

Differences in HOMA-IR were not assessed in this study, as they were in the studies cited,[9,13,18,21] since our samples were from prepubescent children.

According to a study conducted by Almeida et al.,[13] HOMA provides better information for pediatric patients because hyperglycemia is rarely observed at this age. It therefore appears that there is currently a consensus that FI is a reliable parameter for assessing IR in children and that no other parameters are needed. The results of our study also support this statement since it was observed that the Pearson correlation coefficients for the comparison between HOMA-IR and BMI (Pearson's coefficient = 0.326) and for the comparison between insulin and BMI (Pearson coefficient = 0.321) were approximately equal.

In a study published by Silva et al.,[21] correlation coefficients suggested a significant association between BMI and IR. The findings of this study support their results since there was also a significant association between BMI and HOMA-IR.

In children and adolescents, obesity generally precedes the appearance of hyperinsulinism,[22] which is considered an independent risk factor for cardiovascular diseases.[4,9]

Elevated insulin levels are associated with elevated TG levels[4] and with their accumulation in liver and muscle tissues.[22] Data from 2004 indicate that 60% of children and adolescents who are overweight have a least one risk factor for cardiovascular disease.[4]

Obese and overweight people are a heterogeneous subset with a range of metabolic and phenotypical IR expressions. People with the same BMI may have different IR and differing metabolic characteristics.[22]

It is possible that the reason for the positive association between BMI and HOMA-IR is the fact that fat in the mesenteric and omental regions is particularly sensitive to lipolytic stimuli and, in the presence of lypolisis products draining via the hepatic portal circulation, leads to IR by lipotoxicity. Furthermore, because of its high lipolytic capacity and reduced sensitivity to the anti-lipolytic stimulus of insulin, visceral fat also tends to release greater quantities of free fatty acids into the hepatic portal vein.[21] Since male pattern obesity (greater deposition of fat in the abdominal region) has a strong association with metabolic disorders, it is important to investigate body fat distribution and its relationship with the etiology of hyperinsulinism.[4]

Under normal conditions, insulin performs several functions in lipid metabolism regulation. However, the same is not observed in obese people because of the frequent changes that IR causes to the effects of certain enzymes and to lipid metabolism.[4] This, in turn, intensifies oxidation of free fatty acids in serum, provides substrate for TG synthesis in the liver and increases hepatic secretion of very low density lipoproteins, rich in TG, into the serum.[23]

The tragic immediacy of the growing number of people affected by obesity/insulin resistance syndrome demands urgent public health measures directed at early identification and intervention during childhood.[8] The results reported here allow for the conclusion that hyperinsulinism is strongly associated with BMI. Ergo, obese children have greater chances of developing hyperinsulinism and so certain preventative measures are required to avoid excessive weight gain during childhood and adolescence.

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