Predicting insulin resistance in children: anthropometric and metabolic indicators

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Abstract

Objective: To predict insulin resistance in children based on anthropometric and metabolic indicators by analyzing the sensitivity and specificity of different cutoff points.

Methods: A cross-sectional study was carried out of 109 children aged 7 to 11 years, 55 of whom were obese, 23 overweight and 31 well-nourished, classified by body mass index (BMI) for age. Measurements were taken to determine BMI, waist and hips circumferences, waist circumference/hip circumference ratio, conicity index and body fat percentage (dual emission X-ray absorptiometry). Fasting blood samples were taken to measure triglyceridemia, glycemia and insulinemia. Insulin resistance was evaluated by the glycemic homeostasis method, taking the 90th percentile as the cutoff point. Receiver operating characteristic curves were analyzed to a 95% confidence interval in order to identify predictors of glycemic homeostasis, and sensitivity and specificity were then calculated.

Results: After analysis of the area under the receiver operating characteristic curve (confidence interval), indicators that demonstrated the power to predict insulin resistance were, in the following order: insulinemia = 0.99 (0.99-1.00), 18.7 µU·mL^{-1}; body fat percentage = 0.88 (0.81-0.95), 41.3%; BMI = 0.90 (0.83-0.97), 23.69 kg·m$^{2-1}$; waist circumference= 0.88 (0.79-0.96), 78.0 cm; glycemia = 0.71 (0.54-0.88), 88.0 mg·dL^{-1}; triglyceridemia = 0.78 (0.66-0.90), 116.0 mg·dL^{-1} and conicity index = 0.69 (0.50-0.87), 1.23 for the whole sample; and were: insulinemia = 0.99 (0.98-1.00), 19.54 µU·mL^{-1}; body fat percentage = 0.76 (0.64-0.89), 42.2%; BMI = 0.78 (0.64-0.92), 24.53 kg·m$^{2-1}$; waist circumference = 0.77 (0.61-0.92), 79.0 cm and triglyceridemia = 0.72 (0.56-0.87), 127.0 mg·dL^{-1}, for the obese subgroup.

Conclusions: Anthropometric and metabolic indicators appear to offer good predictive power for insulin resistance in children between 7 and 11 years old, employing the cutoff points with the best balance between sensitivity and specificity of the predictive technique.

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Introduction

Insulin resistance is a clinical condition that is character-ized by reduced cellular glucose uptake in response to a given concentration of insulin and which has been identified as a public health problem,[1] while attention has also been called to the condition in populations such as children and adolescents.[2-4] The disorder is associated with a defect in post-receptors of the insulin signaling pathway,[5] which inter-feres with the translocation process of the muscular glucose transporter (GLUT-4), which itself performs an important role

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in glucose uptake. Recently, some authors[6,7] have extrapolated this initial theory and proposed an explanation for insulin resistance based on a lipocentric perspective, by which an accumulation of intramuscular lipids originating from long chain fatty acids penetrating cells would inhibit translocation of GLUT-4 to the plasmatic membrane, thereby also suggesting a possible alternative method of identifying insulin resistance based on indicators associated with body fat content.

The techniques for diagnosing insulin resistance based on biomolecular evaluation of insulin receptors and post-receptors[5] and on the euglycemic-hyperinsulinemic clamp test (which analyzes glucose uptake during induced hyperinsulinemia),[2,8] are expensive and, for many health professionals, difficult to access. Huang et al.[9] validated the glucose homeostasis index (HOMA) for the identification of insulin resistance in children, demonstrating it to be an interesting proposal when compared with the gold standard. Nevertheless, the HOMA calculations require values for fasting insulinemia and glycemia, which in turn demand invasive sample collections. These procedures make the use of this index problematic, especially for the diagnostic evaluation of large population samples.

It is clear that there is a need for diagnostic tests to be developed that are easy to apply, offer good precision and are of low cost, with the objective of predicting insulin resistance based on risk factors.[10] It is a fact that childhood obesity is associated with negative consequences for children's health, and its prevalence has been increasing progressively over recent years.[11-13] In this context, excess body fat is a variable which may have the potential to predict insulin resistance in children.[9,14] To give one example, waist circumference (WC) has been highlighted as an independent predictor of metabolic and hemodynamic disorders.[15,16] However, these studies identified cutoff points for the variable based on the 90th percentile for a given population and further research is required to suggest diagnostic tests and their respective advantages, and with the inclusion of data on the degree of sensitivity and specificity of the methods being proposed.

Although the health sciences have identified indicators based on body composition to predict insulin resistance, diabetes type 2 and other diseases of a cardiovascular character,[16-18] no studies have been carried out with children to investigate indicators with cutoff points determined based on an analysis of the balance between the sensitivity and specificity of the prediction technique. This being so, the objective of this study was to test insulin resistance prediction in children based on anthropometric and metabolic indicators while simultaneously calculating the sensitivity and specificity of cutoff points.

Methods

This was a population-based cross-sectional study of an initial randomized sample selected from the public schools of Taguatinga, a satellite city of Brasília, DF, Brazil, in accordance with a sample size calculation with a confidence interval (CI) of 97%. Schools, grades and classes were chosen at random, preserving the proportionality of the children enrolled in the educational sector chosen for study. The sample analysis had demonstrated that 394 children were needed to achieve a number of participants (p = 0.05) representative of the population of schoolchildren enrolled in the public school system. However, with the intention of guaranteeing a more expressive number, the initial analysis included 958 children from 10 public schools (p = 0.03), observing a prevalence of overweight of 10.6% (n = 102) and of 7.7% (n = 74) of obesity, meaning that 18.3% of the total number of children were overweight. After screening the 958 initial subjects, 109 children of both sexes were chosen with a variety of nutritional status classifications and aged from 7 to 11 years. The sample studied was classified according to body mass index/age (BMI/age),[19] defining 55 children as obese (over the 95th percentile), 23 children as overweight (between percentiles 85 and 95) and 31 children as well-nourished (between percentiles 5 and 75). The number of overweight and obese participants was defined based on the prevalence of overweight and obesity observed previously (18.3%) in this population, and resulting in an estimate that 71 individuals (p = 0.05) would be sufficient to represent the population of overweight and obese children enrolled in the public education system. A further subgroup of 31 children classified as well-nourished comprised the control group, completing the breakdown of the whole sample studied.

The protocol for this research was approved by the Ethics Committee at the Universidade Católica de Brasília (UCB) and by the Taguatinga Regional Education Department (Secretaria Regional de Ensino de Taguatinga). Those responsible for the study participants signed a free and informed consent form giving authorization for the children selected to participate in the study.

The weight, height and BMI[20] of each child were measured using a Plena brand balance with a digital readout and a stadiometer by Seca. Waist circumference and hip circumference (HC) were measured,[20] using a tape measure, Seca brand, and then calculations were performed to obtain the waist-to-hip ratio (WHR)[21] and conicity index (C index),[18] as follows:

$$\text{C index} = \frac{\text{Waist circumference (m)}}{0.109\sqrt{\dfrac{\text{Body weight (kg)}}{\text{Height (m)}}}}$$

Body fat was evaluated using dual emission X-ray absorptiometry (DEXA), with Lunar DPX-IQ apparatus (Lunar Corporation, Madison, WI, United States) with software version

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4.6A. The volunteers were requested to remove all metal objects that they might be wearing or carrying. Each subject was then positioned in decubitus dorsal on the DEXA machine for a whole body scan with the pediatric analysis option selected, in accordance with the manufacturer's recommendations. The equipment had been duly calibrated before use. Fat mass was calculated for each participant in relative terms (%F), and all analyses were carried out by the same researcher.[13]

After an overnight fast of 12 hours, venous blood was taken at the UCB Hospital between 7:45 and 9:00 am for biochemical analysis. The samples were conditioned in vacuum tubes with separator gel and without anticoagulant. After collection, the blood was centrifuged for 10 minutes at 3,000 rpm to separate the serum from the remaining components, and the serum was used for analysis. Triglycerides and blood glucose were assayed using an enzymatic colorimetric kit, processed in an Autohumalyzer A5 (Human-2004). Insulin was assayed using the Automated Chemiluminescence System ACS-180 (Ciba-Corning Diagnostic Corp., 1995, United States).

Insulin resistance was calculated using the HOMA method,[9] as illustrated by the following equation:

$$HOMA = \frac{\text{Insulinemia (μUI/mL) x Glycemia (mmol/L)}}{22.5}$$

The HOMA index has been validated for children by Huang et al.[9] against the euglycemic-hyperinsulinemic clamp technique. The criterion adopted here for a diagnosis of insulin resistance was a HOMA index over the 90th percentile (p. 90), as has been proposed in the past.[22-24]

Receiver operating characteristic (ROC) analysis was adopted to select the cutoff points that identified insulin resistance for each of the indicators studied.[25] For this procedure the sample was divided into a total group (n = 109; 9.24±1.38 years) and a subgroup comprising just the obese children (n = 55; 9.20±1.16 years). Briefly, a ROC curve is generated by plotting sensitivity on the y-axis as a function of [1 - specificity] on the x-axis. Sensitivity is the percentage of individuals who exhibited the outcome (in the case studied here, insulin resistance) and who have been correctly diagnosed by the indicator in question (i.e. true positives), while specificity describes the percentage of individuals who did not exhibit the outcome and were correctly diagnosed by the indicator (i.e. true-negatives). The criterion utilized to choose the cutoff points was to select the values at which sensitivity and specificity were most similar and were not less than 60%. The statistical significance of each analysis was verified by the area under the ROC curve and by the 95% confidence interval (95%CI). Thus, a perfect indicator would offer an area under

the ROC curve of 1.00, while a diagonal line would represent an area of 0.50. For an indicator to be exhibiting any discriminative power its area under the ROC curve must be between 0.50 and 1.00, and the greater the area the greater the indicator's discriminative power. Another way to determine predictive capacity is using the 95%CI, where, for an anthropometric or metabolic indicator to be considered a significant predictor of insulin resistance, the lower limit of the CI (LL-CI) must not be less than < 0.50.[26] Additionally, Pearson's linear correlation test was applied to the relationships between each of the indicators being tested and insulin resistance, to a significance level of p < 0.05. Statistical analysis of the data was carried out using the software programs Stata[tm] version 9.1 and Statistica® version 5.1.

Results

Table 1 lists the areas under the ROC curves for the anthropometric and metabolic insulin resistance predictors together with their respective CIs. Neither the WHR for the whole group or for the obese subgroup, nor the C index or glycemia for the obese subgroup demonstrated significant discriminatory power for insulin resistance (LL-CI < 0.50). In contrast, after analysis of the areas under the ROC curves, the anthropometric indicators C index, BMI, WC and %F for the whole group and BMI, WC and %F for the obese subgroup did prove to be significant predictors of insulin resistance (LL-CI ≥ 0.50). Furthermore, the metabolic indicators glycemia, insulinemia and triglyceridemia, for the whole group, and insulinemia and triglyceridemia, for the group made up of obese children, all demonstrated significant discriminatory power for insulin resistance prediction (LL-CI ≥ 0.50).

With relation to the ROC curves, it is worth drawing attention to the fact that the x-axis represents [1 - specificity] and the y-axis the sensitivity of possible indicators for predicting insulin resistance (reference). Therefore, the points at which the indicators proposed in this study as having predictive power for insulin resistance exhibit the greatest similarity between the two axes (x and y) were defined as cutoff points and these are listed in Table 2. Furthermore, the correlations between these predictors and insulin resistance are also given in Table 2.

Discussion

The principle findings of this study demonstrate the possibility of predicting insulin resistance in children based on anthropometric and metabolic indicators. Analysis of the ROC curves (Table 1), a method not previously used for this purpose, suggests the cutoff points with greatest similarity between sensitivity and specificity, offering information related to the degree of validity of the indicator used in the prediction. The predictors of insulin resistance thus proposed, in decreasing order of sensitivity and specificity, were: insulinemia, %F, BMI, WC, glycemia, triglyceridemia and the C index for the whole sample; and insulinemia, %F, BMI, WC

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Table 1 - Area under the ROC curve and 95%CI for the relationships between anthropometric and metabolic indicators and insulin resistance for the whole group and the obese subgroup

Insulin resistance (HOMA index)	Area under the curve ROC (95%CI)	
	Total (n = 109)	Obese (n = 55)
Anthropometric		
WHR	0.67 (0.46-0.87)	0.55 (0.32-0.78)
C index	0.69 (0.50-0.87)*	0.56 (0.34-0.79)
BMI	0.90 (0.83-0.97)*	0.78 (0.64-0.92)*
WC	0.88 (0.79-0.96)*	0.77 (0.61-0.92)*
%F (DEXA)	0.88 (0.81-0.95)*	0.76 (0.64-0.89)*
	$x^2 = 0.057$	$x^2 = 0.031$
Metabolic		
Glycemia	0.71 (0.54-0.88)*	0.66 (0.47-0.84)
Insulinemia	0.99 (0.99-1.00)*	0.99 (0.98-1.00)*
Triglyceridemia	0.78 (0.66-0.90)*	0.72 (0.56-0.87)*
	$x^2 = 0.000$	$x^2 = 0.000$

%F = body fat percentage; 95%CI = 95% confidence interval; BMI = body mass index; C index = conicity index; DEXA = dual emission X-ray absorptiometry; HOMA = glycemic homeostasis index; ROC = receiver operating characteristic; WC = waist circumference; WHR = waist-to-hip ratio.
*Area under the curve ROC demonstrating discriminatory power for insulin resistance (LL-CI ≥ 0.50).

and triglyceridemia for the subgroup composed of obese children (Table 2).

The euglycemic-hyperinsulinemic clamp test has been described as being the gold standard for the identification of insulin resistance in children and adolescents.[2,9,17] It was not possible to use the euglycemic-hyperinsulinemic clamp technique to test for insulin resistance in this study, and the HOMA index was used instead, which could be characterized as a limitation. However, Huang et al.[9] have validated the HOMA technique for identifying insulin resistance in children, and several authors[22-24] have used the index successfully. Despite the practicality of using HOMA when compared with the gold standard, it is still necessary to measure two variables in order to calculate it (glycemia and insulinemia), and these are obtained invasively. Furthermore, measuring insulinemia is

Table 2 - Cutoff points, correlation, sensitivity and specificity of the anthropometric and metabolic indicators for predicting insulin resistance in the whole group (n = 109) and the obese subgroup (n = 55)

Insulin resistance (HOMA index)	Cutoff point		Sensitivity (%)		Specificity (%)	
	Total	Obese	Total	Obese	Total	Obese
Anthropometric						
C index	1.23 (r = 0.39)*	NP	63.64	NP	63.27	NP
WC (cm)	78.0 (r = 0.67)*	79.0 (r = 0.57)*	81.82	63.64	77.55	63.64
BMI (kg/m^2)	23.69 (r = 0.66)*	24.53 (r = 0.54)*	81.82	72.73	79.59	72.73
%F (DEXA)	41.30 (r = 0.57)*	42.20 (r = 0.43)*	90.91	72.73	83.67	72.73
Metabolic						
Glycemia (mg·dL^{-1})	88.00 (r = 0.37)*	NP	72.70	NP	73.50	NP
Insulinemia (µU·mL^{-1})	18.70 (r = 0.99)*	19.54 (r = 0.99)*	100.00	90.91	96.90	93.18
Triglyceridemia (mg·dL^{-1})	116.00 (r = 0.47)*	127.00 (r = 0.46)*	63.60	63.64	67.30	63.64

%F = body fat percentage; BMI = body mass index; C index = conicity index; DEXA = dual emission X-ray absorptiometry; HOMA = glycemic homeostasis index; WC = waist circumference.
* p < 0.05 for the correlation between insulin resistance and the predictor; NP = indicator not predictive of insulin resistance (see LL-CI < 0.50 in Table 1).

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considered difficult to apply within the daily practice of many different health professionals, since biochemical assays are needed that must be carried out in a laboratory environment by a fully trained technician.

Many studies[15,18,23,27] have attempted to identify practical and precise indices for predicting diseases, including insulin resistance,[9,16,17] which may later trigger diabetes type 2 early in life.[28] Information related to detection of insulin resistance during childhood, acquired in a simple and inexpensive manner, can be of benefit to a variety of professionals working with child health during their prophylactic and therapeutic practice, in addition to reducing healthcare costs.

In this study it was possible to identify predictors of insulin resistance based on a single metabolic measurement, such as glycemia, triglyceridemia or insulinemia itself. As would be expected, insulinemia demonstrated the greatest predictive power when its area under the ROC curve was analyzed[25,26] (Table 1), in addition to a high correlation and better sensitivity and specificity when compared with the other indicators (Table 2). On the other hand, triglyceridemia and glycemia, although having lower percentages for sensitivity and specificity when compared with insulinemia (Table 2), proved to be good predictors of insulin resistance. When the area under the ROC curve[25] and the CI were analyzed, in particular the CI lower limit greater than 0.50, it was confirmed that there was a significant predictive ability[26] for glycemia for the whole sample and for triglyceridemia for both the whole sample and for the obese subgroup (Table 1). Nowadays, triglyceridemia and glycemia can be tested using low cost portable analyzers, making it easily possible to use these measurements for the prediction of insulin resistance in children.

Furthermore, anthropometric indicators such as %F, the C index, BMI and WC, also demonstrated significant predictive power[25,26] for insulin resistance (Table 1). Notwithstanding, %F was measured using DEXA, an expensive method that is highly complex to apply clinically. However, similar results are observed when the areas under the ROC curves for the indicators BMI and WC are analyzed with relation to the area under the ROC curve for %F as measured by DEXA, for the whole group and the obese subgroup (Table 1). Furthermore, there were significant moderate to high correlations between %F measured by DEXA and BMI ($r = 0.89$), WC ($r = 0.84$) and the C index ($r = 0.53$) in this study, and with BMI ($r = 0.73$) and WC ($r = 0.61$) in a study by Gomes et al.[27] The power of the variable WC to predict insulin resistance that was detected for both groups in this study (Tables 1 and 2), is in keeping with other studies[10,15,16] that have demonstrated that this variable is an independent predictor, in a variety of populations, for insulin resistance, lipid content and arterial blood pressure. It is therefore suggested that the anthropometric indicators studied here be used for predicting insulin resistance in children, since they offer the advantages of ease of measurement, low cost, a noninvasive nature and values referring to the degree of sensitivity and specificity of the cutoff point proposed.

Currently, in places where morphophysiological, postural and nutritional characteristics are assessed, such as at sports clubs, gymnasiums and physiotherapy, nutrition and pediatrics consulting rooms, there is an ever rising prevalence of patients with a variety of risk factors, of which obesity is of greatest prominence,[11,12,29] which is itself associated with insulin resistance at early ages.[13,14,16] This being so, the practicality of using the indicators proposed here represents easily applied procedures and great clinical importance for future therapeutic and preventative interventions. These practices are even more relevant to the assessment of children, since they make it possible to prevent the complications associated with insulin resistance and diabetes type 2 in later life.

Based on the results observed, we conclude that it has been possible to identify anthropometric and metabolic indicators with discriminatory power for the prediction of insulin resistance in children aged 7 to 11 years, based on the cutoff points with the best balance between sensitivity and specificity. The predictors of insulin resistance proposed were insulinemia, %F, BMI, WC, glycemia, triglyceridemia and the C index for the whole sample, and insulinemia, %F, BMI, WC and triglyceridemia for the subgroup of obese children. The ease with which the indicators proposed can be measured makes them important tools to be used in the routines of health professionals. Further studies with similar methodologies are needed to examine the application of these indicators to different populations and to stratify them by characteristics such as ethnicity and family history of diabetes type 2.

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