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Evaluation of postprandial to fasting insulin ratio as a biochemical marker of insulin resistance in obese Indian children

Abstract

Background: Insulin resistance in childhood obesity is a well recognised and worrisome

complication. Reliable measurements of insulin resistance require invasive or multiple sampling procedures or complex mathematical calculations which are difficult to practice in routine office practice.

Objective: This observational study was aimed to evaluate a simple ratio of 120 minute post

glucose load (OGTT) insulin to fasting insulin for diagnosis of insulin resistance in obese children having clinical markers of insulin resistance and with a HOMA-IR value suggestive of insulin resistance for age and sex.

Methods: Forty Eight obese children and adolescents (35 girls and 34 boys; mean age 10.19 ±

4.23 years and mean BMI 26.17 ± 3.76) were included in the study. All participants underwent an OGTT. Blood samples were obtained 0 and 120 minutes after oral glucose administration for glucose and insulin measurements, and 2 separate groups were studied in both pubertal and pre-pubertal age group, according to the presence or absence of insulin resistance as per the standard HOMA-IR cut-offs. The ratio of 120 minute and fasting insulin, measurements was termed as insulin resistance Index (Ri) and was calculated for both pre-pubertal and pubertal children with insulin resistance. The accuracy of this measurement in measuring Insulin Resistance and the optimal insulin resistance index (Ri) for diagnosis of insulin resistance was established with a receiver operating characteristic (ROC) curve.

Results: The area under the curve for pre-pubertal children was 0.7(close to upper left) and

yielded a sensitivity of 76% and specificity of 70% at Ri value of 4.7. The value of positive likelihood ratio comes at 2.53, pretest probability of 0.61, pretest odds of 1.56, post-test odds of 3.95 and post-test probability of 0.78. However ROC plot had area under the curve of only 0.3 in pubertal children (close to bottom right).

Conclusion: Ri is a sensitive and specific test for calculation of insulin resistance in pre pubertal

children but not accurate in pubertal children.

Keywords: childhood obesity, insulin resistance, insulin resistance index, oral glucose tolerance

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Abbreviations: HOMA-IR, homeostasis model assessment for insulin resistance; OGTT, oral glucose tolerance test; FGIR, fasting glucose/insulin ratio; ROC, receiver operating characteristic; Ri, resistance index

Introduction

Obesity in children is reaching epidemic proportions and is rapidly emerging as the most important chronic disease in childhood.[1] It is common knowledge that obesity is associated with an increased risk for metabolic complications, such as insulin resistance, glucose intolerance and type 2 diabetes mellitus (T2DM). Insulin resistance in adults has been shown to be a cardinal feature in the development of type 2 diabetes.[2] Insulin resistance in children is the most common metabolic alteration related to obesity [3] and is significantly related to cardio metabolic risk.[4]

The standard technique for assessment of insulin sensitivity is the hyperinsulinemic euglycemic clamp. Although recognised as the ultimate gold standard, it is too invasive, cumbersome and expensive for epidemiological or routine clinical use. On the other hand the oral glucose tolerance test (OGTT) is better suited for assessment of large populations as it is relatively non invasive, a minimal risk procedure and practical for office setting.

In the search for a non-invasive measurement technique for insulin sensitivity, several surrogate markers derived from OGTT have been proposed, and each has correlated reasonably well with clamp techniques.[5–8] The homeostatic model assessment (HOMA), fasting insulin, and fasting glucose/insulin ratio (FGIR) have been the most frequently used techniques in clinical investigations. The fact that these tests require only a single venipuncture in the fasting state makes them particularly attractive. Though fasting insulin has been shown to correlate with the euglycemic clamp technique, one of the most widely accepted methods,[6] Homeostatic model assessment,[9] derived from the product of fasting insulin and glucose concentrations, has been shown to be an improvement on fasting insulin alone.[10] In The HOMA approach, rather than using fasting insulin levels or FGIR, the product of the fasting concentrations of glucose (milligrams per deciliter) and insulin (milliunits per milliliter) is divided by a constant 405. Unlike insulin levels and the FGIR, the HOMA calculation compensates for fasting hyperglycaemia.[7] Apart from the criticism that such fasting tests are best suited to large studies; a further problem is that these tests reflect insulin action in an unstimulated or basal state, whereas in life much of insulin action is postprandial. Hence the interest in studying the degree of post-prandial rise in insulin as a marker for insulin resistance. Recently, "2-hour post-glucose insulin level" has been recognized as a possible indicator of insulin resistance in the PCOS patients.[11]

We hypothesized that the extent of rise of insulin in the stimulated state can be used as a biochemical marker of insulin resistance. Objective of the study was to examine whether the ratio of postprandial (1.75gm/kg glucose load) insulin to fasting insulin (i_{120}/i_0) can be used as a biochemical marker of insulin resistance. For the purpose of this study, we took HOMA-IR as the gold standard for measurement of insulin resistance in office practice.

Materials and methods

Forty eight obese children and adolescents (35 girls and 34 boys; mean age 10.19±4.23 years and mean BMI 26.17±3.76) participated in this observational study. All children and adolescents were recruited from the Department of Pediatric Endocrinology of Manipal Hospital Bengaluru between November 2012 and February 2015. Majority of the source population belonged to the relatively affluent population of Bengaluru. BMI was calculated as weight (in kilograms) divided by height (in meters) squared. Subjects with a BMI above the 95th percentile for age and gender as per year 2000 growth charts by the Centres for Disease Control and Prevention were classified as obese. Detailed medical and family histories were obtained for all subjects, and physical examinations were performed. The findings were recorded in printed questionnaires. The exclusion criteria included subjects with any co-morbidity or chronic illness and those who do not turn up for the blood tests. All included subjects were healthy and had normal thyroid function. Parents provided informed consent and children and adolescents provided informed assent before testing commenced. The study was approved by the institutional ethics committee.

After a 3-day, high-carbohydrate diet and an overnight fast, a standard OGTT (1.75 g/kg or a maximum of 75 g of glucose) was performed for all subjects. Blood samples were obtained 0, and 120 minutes after glucose administration for glucose and insulin measurements were also performed on those samples. Plasma glucose levels were measured with the glucose oxidase method and insulin levels were determined by electrochemiluminescence immunoassay (ECLIA) by Cobas 601 analyser with lower detection limit of 0.2 mIU/mL. The HOMA index was calculated as fasting insulin concentration (mIU/mL) multiplied by fasting glucose concentration (mg/dL) and the product divided by 405, assuming that normal young subjects have an insulin resistance of 1. There were no missing values of glucose or insulin.

We divided the subjects into groups with insulin resistance and without insulin resistance by using HOMA-IR cut-off points of 2.62 (sensitivity 88.2%, specificity 65.5%) and 2.22 (sensitivity 100%, specificity 42.3%) for prepubertal boys and girls respectively, and 5.22(sensitivity 56%, specificity 93%) and 3.82 (sensitivity 77.1%, specificity 71.4%) for pubertal boys and girls respectively. Although some studies have recommended a lower level of HOMA-IR as the cut off, we chose to keep higher cut-offs to increase the specificity of the diagnosis.[12] We used the term insulin resistance index (Ri) for the ratio of 120 minute post glucose load insulin to fasting insulin value.

Statistical analyses

Analyses were performed with SPSS version 20 software for Windows. Data are as mean +/- Standard Deviation. The optimal insulin resistance index (Ri) for diagnosis of insulin resistance was established with a receiver operating characteristic (ROC) curve, whereby equal weight was given to the sensitivity and the specificity of the test. To calculate the sensitivity and specificity of diagnostic test, we used this cut-off point on the curve. In a ROC curve, the true-positive rate (sensitivity) is plotted as a function of the false-positive rate (1-specificity) for different cut-off points. Each point on the ROC plot represents a sensitivity/ specificity pair corresponding to a particular decision threshold. A test with perfect discrimination has a ROC plot that passes through the upper left corner (100% sensitivity and 100% specificity). Therefore, the closer the ROC plot is to the upper left corner, the greater is the overall accuracy of the test.[13]

Results

The study group consisted of 48 children. The baseline characteristics of the subjects were as in (Table 1). We divided both pre-pubertal and pubertal subjects into two groups depending on the presence or absence of insulin resistance as per age and sex related HOMA-IR cut offs. The physical characteristics and the biochemical investigation values of both groups are depicted in (Table 2) & (Table 3).

Sensitivity and specificity calculations were based on ROC analysis of the resultant values of Insulin resistance Index with respect to the presence or absence of insulin resistance as calculated by the HOMA-IR method. The ROC plot for insulin Resistance index is closer to the upper left corner when plotted for pre-pubertal children, indicating greater overall accuracy of the test for this study population (Figure 1). The area under the curve is 0.7 indicating good accuracy for this age group. However ROC plot for insulin Resistance index is closer to the lower right corner when plotted for pubertal children and has an area under the curve of 0.3 indicating poor accuracy of the test for this age group (Figure 2). The optimal Ri value for diagnosis of insulin resistance in prepubertal children was established on a ROC scatter plot by determining the optimal decision point from the ROC curve, whereby equal weight was given to the sensitivity and the specificity of the test. The sum of the sensitivity and specificity values was highest at the insulin Ri value of 4.7. This value has yielded a sensitivity of 76% and specificity of 70%. The value of positive likelihood ratio comes at 2.53, pretest probability of 0.61, pretest odds of 1.56, post-test odds of 3.95 and post-test probability of 0.78.

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Table 1: Characteristics of Study Population

	Prepubertal	Pubertal
Number	34	15
Age	8.5 ± 4.01	13.66 ± 1.96
M/F	17/17	7/8
BMI	25.197 ± 3.60	2.35 ± 3.27
FG	87 ± 7.5	83.93 ± 9.01
PPG	108.5 ± 18.24	111.26 ± 27.48
FI	19.729 ± 11.89	25.57 ± 11.21
PPI	115.62 ± 98.05	172.80 ± 139.32
FGIR	6.70 ± 4.85	3.92 ± 1.73
HOMA-IR	4.26 ± 2.58	5.39 ± 2.55
Insulin Resistance index (Ri)	5.50 ± 2.59	7.39 ± 5.26

Abbrevations: BMI, body mass index; FG, fasting glucose; PPG, post prandial glucose; FI, fasting insulin; PPI, post prandial insulin; FGIR, fasting glucose insulin ratio; HOMA-IR, homeostasis model assessment for insulin resistance.

Table 2: Characteristics of Pre-Pubertal Subjects

	With insulin resistance	Without insulin resistance
Number	21	13
Age	10.2 ± 3.67	5.78 ± 2.93
Male/Female	8/13	9/4
Weight	53.1 ± 15.67	41.62 ± 29.16
BMI	26.53 ± 3.18	23.07 ± 3.27
FG	87.86 ± 8.38	85.62 ± 6.11
PPG	115.05 ± 18.11	97.92 ± 13.12
FI	24.64 ± 7.89	11.79 ± 13.21
PPI	150.75 ± 80.94	58.87 ± 99.36
FGIR	3.96 ± 1.43	11.14 ± 5.171
HOMA-IR	5.29 ± 1.58	2.59 ± 3.05
Insulin Resistance Index (Ri)	6.06 ± 2.44	4.60 ± 2.66

Abbrevations: BMI, body mass index; FG, fasting glucose; PPG, post prandial glucose; FI, fasting insulin; PPI, post prandial insulin; FGIR, fasting glucose insulin ratio; HOMA-IR, homeostasis model assessment for insulin resistance.

Table 3: Characteristics of Pre-Pubertal Subjects.

	With insulin resistance	Without insulin resistance
Number	8	6
Age	14.43 ± 1.58	12.63 ± 2.08
M/F	4/4	3/3
Weight	73.73 ± 11.82	67.06 ± 7.85
BMI	29.72 ± 2.85	26.52 ± 3.06
FG	87.75 ± 8.61	78.83 ± 7.27
PPG	110.25 ± 29.11	112.6 ± 27.80
FI	32.90 ± 8.37	15.81 ± 5.34
PPI	181.15 ± 132.58	161.68 ± 160.01
FGIR	2.81 ± 0.74	5.40 ± 1.56
HOMA-IR	7.13 ± 1.81	3.10 ± 1.15
Insulin Resistance Index (Ri)	5.64 ± 3.61	9.731 ± 6.50

Abbrevations: BMI, body mass index; FG, fasting glucose; PPG, post prandial glucose; FI, fasting insulin; PPI, post prandial insulin; FGIR, fasting glucose insulin ratio; HOMA-IR, homeostasis model assessment for insulin resistance.

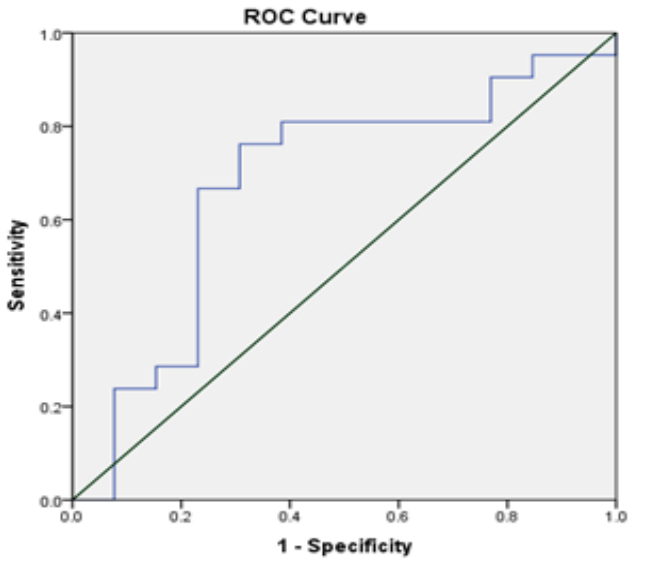

Figure 1: ROC curve for Ri in pre-pubertal children.

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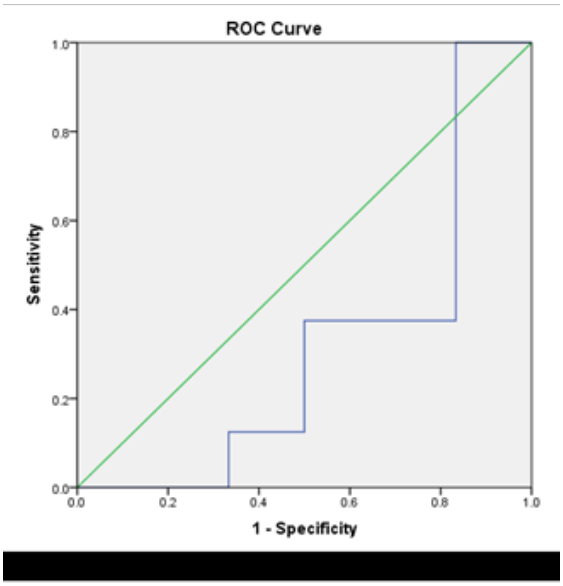

Figure 2: ROC curve for Ri in pubertal children.

Discussion

This study demonstrates that Insulin resistance index (ratio of postprandial to fasting insulin) has high sensitivity and specificity for measuring insulin resistance in prepubertal obese children. Previous studies have evaluated various indices for evaluation of insulin resistance in office setting using values derived from standard OGTT. With the exceptions of HOMA-IR, fasting insulin and fasting glucose insulin ratio, the other indices either require invasive/frequent sampling for insulin or not so simple mathematical calculations. Also, most indices in clinical use utilise fasting insulin values while in life, most of the insulin is postprandial. We evaluated the ratio of 120 minute insulin value to fasting insulin value (we termed it Insulin Resistance index (Ri)). Its performance as a diagnostic test was evaluated using a proven index of insulin sensitivity (HOMA-IR) and using a Receiver Operating Characteristic (ROC) curve analysis. The ROC plot for insulin Resistance index is closer to the upper left corner when plotted for pre-pubertal children, indicating greater overall accuracy of the test for this study population. The optimal Ri value was chosen giving equal weight to sensitivity and specificity. The cut off of 4.7 yielded a sensitivity of 76 % and specificity of 70 %. The value of positive likelihood ratio comes at 2.53, pre-test probability of 0.61, pre-test odds of 1.56, post-test odds of 3.95 and post-test probability of 0.78. Hence the insulin Resistance Index performed well as a diagnostic test for insulin resistance in pre-pubertal obese children with clinical signs of insulin resistance.

However when plotted for pubertal children, the proposed index performed with a poor accuracy yielding a ROC plot closer to the bottom right corner of the axes and very low area under the curve. Though it can be postulated to result from a higher basal insulin secretion in puberty because of physiologic insulin resistance, larger and more focussed studies on insulin pharmacodynamics in puberty is needed to reach a conclusion. Further studies are also needed to compare Insulin Resistance Index with HOMA-IR as a tool for diagnosis of Insulin Resistance in office practice. The cut-off values of HOMA-IR used for diagnosing insulin resistance in this study were generated in Turkish Children. Therefore further evaluation of Insulin Ri with respect to cut-offs in the South east Asian population can be an improvement in the study. The value of insulin at two hours post glucose load was chosen as a convenient extension to a standard OGTT. We cannot comment on whether the peak at two hours is the optimum value to be used as the numerator in calculation of the 'rise' of insulin under glucose stress in suspected insulin resistance. Combination of this study with clamp studies can suggest improvement in the time of post-pradial sampling.

Conclusion

Insulin Resistance Index (Ri) is a sensitive and specific marker that can be used as a tool to diagnose insulin resistance in prepubertal children in epidemiology and office practice due to the ease in determination. The use of Ri can be a simpler, cheaper, less labour-intensive, less time-consuming, and more acceptable alternative to patients and care providers than other invasive and complex indices. However the test is not accurate in pubertal obese children. This study also demonstrates that the Ri cut-off point for diagnosis of insulin resistance is 4.7 for prepubertal children. Further studies are needed to validate Insulin Resistance index for diagnosis of Insulin resistance in obese children and improve upon its sensitivity and specificity.

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None.

Conflicts of interest

The author declares there is no conflict of interest.

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