

# Homeostasis Model Assessment Is More Reliable Than the Fasting Glucose/Insulin Ratio and Quantitative Insulin Sensitivity Check Index for Assessing Insulin Resistance Among Obese Children and Adolescents

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**ABSTRACT.** *Objective.* Simple fasting methods to measure insulin resistance, such as the homeostasis model assessment (HOMA), fasting glucose/insulin ratio (FGIR), and quantitative insulin sensitivity check index (QUICKI) methods, have been widely promoted for adult studies but have not been evaluated formally among children and adolescents. The aim of this study was to compare the HOMA, FGIR, and QUICKI methods for measuring insulin resistance, expressed by oral glucose tolerance test (OGTT) results, among obese children and adolescents.

*Methods.* Fifty-seven pubertal obese children and adolescents (30 girls and 27 boys; mean age,  $12.04 \pm 2.90$  years; mean BMI:  $29.57 \pm 5.53$ ) participated in the study. All participants underwent an OGTT. Blood samples were obtained 0, 30, 60, 90, and 120 minutes after oral glucose administration for glucose and insulin measurements, and 2 separate groups were studied, according to the presence or absence of insulin resistance. HOMA, FGIR, and QUICKI methods were studied for validation of insulin resistance determined with the OGTT for these groups.

*Results.* The groups consisted of 25 obese children and adolescents with insulin resistance (14 girls and 11 boys; mean age:  $12.88 \pm 2.88$  years; mean BMI:  $31.29 \pm 5.86$ ) and 32 subjects without insulin resistance (16 girls and 16 boys; mean age:  $11.38 \pm 2.79$  years; mean BMI:  $28.23 \pm 4.94$ ). There were significant differences in the mean HOMA ( $6.06 \pm 4.98$  and  $3.42 \pm 3.14$ , respectively) and QUICKI ( $0.313 \pm 0.004$  and  $0.339 \pm 0.004$ , respectively) values between the 2 groups. Sensitivity and specificity calculations based on insulin resistance with receiver operating characteristic curve analysis indicated that HOMA had high sensitivity and specificity for measuring insulin resistance.

*Conclusions.* As a measure of insulin resistance among children and adolescents, HOMA is more reliable than FGIR and QUICKI. The present HOMA cutoff point for diagnosis of insulin resistance is 3.16. The HOMA cutoff point of  $>2.5$  is valid for adults but not for adolescents. *Pediatrics* 2005;115:e500–e503. URL: [www.pediatrics.org/cgi/doi/10.1542/peds.2004-1921](http://www.pediatrics.org/cgi/doi/10.1542/peds.2004-1921); *insulin resistance, children, adolescents.*

**ABBREVIATIONS.** HOMA, homeostasis model assessment; OGTT, oral glucose tolerance test; FGIR, fasting glucose/insulin ratio; QUICKI, quantitative insulin sensitivity check index; ROC, receiver operating characteristic.

Insulin resistance is the greatest risk factor for the development of type 2 diabetes and is perhaps the greatest current health threat to our children. The prevalence of childhood obesity has more than doubled in the past 15 years in many regions of the world.<sup>1–5</sup> The marked increase in pediatric obesity in the past decade has resulted in unprecedented increases in the incidence of type 2 diabetes mellitus among children and adolescents. In these grossly obese children, both insulin resistance and impaired insulin secretion contribute to the increase in glucose levels, and the degree of obesity is related to cardiovascular risk factors independent of insulin resistance.<sup>2–4</sup>

The standard technique for assessment of insulin sensitivity is the hyperinsulinemic euglycemic clamp; it is often combined with the hyperglycemic clamp to determine the adequacy of compensatory  $\beta$ -cell hypersensitivity.<sup>6–9</sup> Although clamp technology has been applied to the study of insulin sensitivity and insulin secretion during childhood, it is too invasive for general epidemiologic studies. Because no intravenous access is needed, the oral glucose tolerance test (OGTT) is better suited for assessment of large populations. Although OGTTs are more difficult to perform than simple measurements of fasting glucose and insulin levels, the OGTT is a minimal-risk procedure that is applicable for large-scale screening and for repeat studies for individual subjects.<sup>10</sup>

In the quest for a noninvasive measurement technique for insulin sensitivity, several fasting or “homeostatic” models have been proposed, and each has correlated reasonably well with clamp techniques.<sup>11–13</sup> The homeostatic model assessment (HOMA), fasting glucose/insulin ratio (FGIR), and quantitative insulin sensitivity check index (QUICKI) methods have been the most frequently used techniques in clinical investigations. The fact that these tests require only a single venipuncture in the fasting state and do not call for concomitant intravenous access makes them particularly attractive to patients and clinicians alike.

The HOMA approach has been widely used in clinical research to assess insulin sensitivity.<sup>9,14</sup>

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Rather than using fasting insulin levels or FGIR, the product of the fasting concentrations of glucose (expressed as milligrams per deciliter) and insulin (expressed as milliunits per milliliter) is divided by a constant. The constant 405 should be replaced by 22.5 if the glucose concentration is expressed in Système International units. Unlike insulin levels and the FGIR, the HOMA calculation compensates for fasting hyperglycemia.<sup>13</sup> The HOMA and insulin values increase for insulin-resistant patients, whereas the FGIR decreases.

The QUICKI method can be applied to normoglycemic and hyperglycemic patients. The index is derived by calculating the inverse of the sum of logarithmically expressed fasting glucose and insulin concentrations.<sup>13</sup> As insulin concentrations decrease, QUICKI values increase.

## METHODS

### Research Design and Methods

Fifty-seven pubertal obese children and adolescents (30 girls and 27 boys; mean age:  $12.04 \pm 2.90$  years; mean BMI:  $29.57 \pm 5.53$ ) participated in the study. All children and adolescents were recruited from the Department of Pediatric Endocrinology of Erciyes University Faculty of Medicine. BMI was calculated as weight (in kilograms) divided by height (in meters) squared. All subjects had a BMI above the 95th percentile for age and gender and thus were classified as obese. On the basis of the year 2000 growth charts, this BMI category is referred to as overweight by the Centers for Disease Control and Prevention. Detailed medical and family histories were obtained for all subjects, and physical examinations were performed. All subjects were healthy and had normal thyroid function. Parents provided informed consent and children and adolescents provided informed assent before testing commenced.

We divided the subjects into groups with insulin resistance and without insulin resistance by using a cutoff point of the sum of insulin levels during the OGTT of  $300 \mu\text{U}/\text{mL}$ .<sup>15,16</sup> After a 3-day, high-carbohydrate diet (300 g/day) 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, 30, 60, 90, and 120 minutes after glucose administration, for glucose and insulin measurements. Plasma glucose levels were measured with the glucose oxidase method and a modified Trinder color reaction, catalyzed by the peroxidase enzyme, and insulin levels were measured with an immunoradiometric assay kit.

### Indexes Derived From Fasting Blood Samples

The HOMA index, QUICKI, and FGIR were derived as estimates of insulin resistance. The HOMA index was calculated as fasting insulin concentration ( $\mu\text{U}/\text{mL}$ )  $\times$  fasting glucose concentration (mmol/L)/22.5, assuming that normal young subjects have an insulin resistance of 1. The QUICKI was calculated as  $1/[\log \text{fasting insulin concentration } (\mu\text{U}/\text{mL}) + \log \text{glucose concentration } (\text{mg}/\text{dL})]$ .

## Statistical Analyses

Analyses were performed with SPSS version 10 software for Windows (SPSS, Chicago, IL). Data are reported as means  $\pm$  SD and ranges. We compared groups by using independent-sample *t* tests.  $P < .05$  was considered significant for all data analyses. The optimal HOMA value for diagnosis of insulin resistance was established with a receiver operating characteristic (ROC) scatter plot. An alternative way to establish an optimal cutoff value for a test is to determine the optimal decision point from an ROC curve, whereby equal weight is given to the sensitivity and the specificity of the test. To calculate the sensitivity and specificity of diagnostic tests, we used this cutoff point. The sensitivity and specificity of insulin resistance indexes were estimated as true-positive results/(true-positive results + false-negative results) and true-negative results/(true-negative results + false-positive results), respectively. In a ROC curve, the true-positive rate (sensitivity) is plotted as a function of the false-positive rate ( $1 - \text{specificity}$ ) for different cutoff 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.<sup>17,18</sup>

## RESULTS

The groups consisted of 25 obese children and adolescents with insulin resistance (14 girls and 11 boys; mean age:  $12.88 \pm 2.88$  years; mean BMI:  $31.29 \pm 5.86$ ) and 32 subjects without insulin resistance (16 girls and 16 boys; mean age:  $11.38 \pm 2.79$  years; mean BMI:  $28.23 \pm 4.94$ ) (Table 1). The mean fasting glucose level was  $82.67 \pm 9.23 \text{ mg}/\text{dL}$  (range: 65–106 mg/dL), the mean fasting insulin level was  $26.98 \pm 22.49 \mu\text{U}/\text{mL}$  (range: 1.45–109.72  $\mu\text{U}/\text{mL}$ ), and the mean sum of insulin levels was  $447.32 \pm 145.22 \mu\text{U}/\text{mL}$  (range: 300.24–744.39  $\mu\text{U}/\text{mL}$ ) for the group with insulin resistance; the mean fasting glucose level was  $80.44 \pm 10.51 \text{ mg}/\text{dL}$  (range: 61–105 mg/dL), the mean fasting insulin level was  $16.65 \pm 13.85 \mu\text{U}/\text{mL}$  (range: 1.40–51.47  $\mu\text{U}/\text{mL}$ ), and the mean sum of insulin levels was  $154.08 \pm 77.78 \mu\text{U}/\text{mL}$  (range: 24.86–275.00  $\mu\text{U}/\text{mL}$ ) for the group without insulin resistance (Table 1). There were significant differences in the mean HOMA ( $6.06 \pm 4.98$  and  $3.42 \pm 3.14$ ,  $P < .05$ ) and QUICKI ( $0.313 \pm 0.004$  and  $0.339 \pm 0.004$ ,  $P < .05$ ), but not FGIR, values between the 2 groups (Table 2).

Sensitivity and specificity calculations were based on insulin resistance with ROC analysis. 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). The ROC plot for

**TABLE 1.** Physical Characteristics of the Study Population

|  | Obese Subjects With Insulin Resistance* | Obese Subjects Without Insulin Resistance |
|--|---|---|
| No.  | 25                                      | 32  |
| Age, y   | $12.88 \pm 2.88$                        | $11.38 \pm 2.79$                          |
| Gender, M/F                                    | 11/14                                   | 16/16                                     |
| BMI, kg/m <sup>2</sup>                         | $31.29 \pm 5.86$                        | $28.23 \pm 4.94$                          |
| Fasting glucose level, mg/dL                   | $82.67 \pm 9.23$ (65–106)               | $80.44 \pm 10.51$ (61–105)                |
| Fasting insulin level, $\mu\text{U}/\text{mL}$ | $26.98 \pm 22.49$ (1.45–109.72)         | $16.65 \pm 13.85$ (1.40–51.47)            |
| Sum of insulin levels, $\mu\text{U}/\text{mL}$ | $447.32 \pm 145.22$ (300.24–744.39)     | $154.08 \pm 77.78$ (24.86–275.00)         |

Data are expressed as mean  $\pm$  SD (range).

\* During OGTT, sum of insulin levels of  $>300 \mu\text{U}/\text{mL}$ .

**TABLE 2.** Indexes of Insulin Resistance

|        | Obese Subjects With Insulin Resistance | Obese Subjects Without Insulin Resistance |
|--------|--|---|
| No.    | 25                                     | 32  |
| FGIR   | 6.64 ± 11.76 (0.72–59.59)              | 8.66 ± 8.47 (1.67–47.14)                  |
| HOMA   | 6.06 ± 4.98 (0.30–21.33)*              | 3.42 ± 3.14 (0.23–12.70)*                 |
| QUICKI | 0.313 ± 0.004 (0.254–0.475)*           | 0.339 ± 0.004 (0.270–0.509)*              |

Data are expressed as mean ± SD (range).

\*Significant at  $P < .05$ .

HOMA is closer to the upper left corner, indicating greater overall accuracy of the test (Fig 1). The optimal HOMA value for diagnosis of insulin resistance was established on a ROC scatter plot by determining the optimal decision point from the ROC curve, whereby equal weight is given to the sensitivity and the specificity of the test. The sum of the sensitivity and specificity values is highest at this point. To calculate the sensitivity and specificity of diagnostic tests, we used this cutoff point. HOMA had high sensitivity and specificity for measuring insulin resistance. The present HOMA cutoff point for diagnosis of insulin resistance of 3.16 yielded a sensitivity of 76% and a specificity of 66%.

### DISCUSSION

This study demonstrates that HOMA has high sensitivity and specificity for measuring insulin resistance. Previous studies evaluated simple indexes for assessing insulin sensitivity in a wide range of conditions associated with insulin resistance. This study was a unique presentation. HOMA, FGIR, and QUICKI for measuring insulin resistance expressed by OGTT results among obese children and adolescents were compared by using sensitivity and specificity calculations based on insulin resistance with ROC analysis. ROC curves can be used to compare the diagnostic performance of  $\geq 2$  laboratory or diagnostic tests.<sup>19</sup>

The FGIR was found to be a highly sensitive and specific measure of insulin sensitivity.<sup>11,20</sup> The mean FGIR value was  $<7$  for the study group with insulin resistance, as we expected, but the difference between the 2 groups was not statistically significant and the SD was large. One of the explanations for interpreting the FGIR might be higher basal insulin levels among obese pubertal children and adoles-

cents, and another might be emotional stress at the time of the blood test.<sup>11</sup> Therefore, we designed statistical analyses with ROC plots to compare the diagnostic performance of diagnostic tests, and we found that HOMA had high sensitivity and specificity for measuring insulin resistance. We suggested that misclassification as insulin resistance with the HOMA was less.

The present study also demonstrated that the HOMA cutoff point for diagnosis of insulin resistance was 3.16. Insulin resistance was defined by Reinehr et al<sup>21</sup> as a HOMA value of  $>4$  for adolescents. This point was determined to be 2.5 for adults.<sup>22</sup>

Insulin resistance is a state in which normal concentrations of insulin produce a subnormal biologic response. There has been considerable interest in the childhood development of insulin resistance, hyperlipidemia, ovarian hyperandrogenism, and early markers of adult diseases such as type 2 diabetes mellitus, hypertension, and cardiovascular disease. Patients with insulin resistance have hyperinsulinemia together with normoglycemia or hyperglycemia. Insulin resistance is commonly associated with obesity. The central role of insulin in the clustering of some cardiovascular risk factors was first suggested by reports of endogenous hyperinsulinemia and insulin resistance in essential hypertension. Insulin is the central regulator of glucose and lipid homeostasis. Insulin decreased blood glucose concentrations by reducing hepatic gluconeogenesis and glycogenolysis and by enhancing glucose uptake into striated muscles and adipocytes. Insulin also enhances triglyceride (triacylglycerol) synthesis in liver and adipose tissues, increases the breakdown of circulating lipoproteins by stimulating lipoprotein lipase activ-

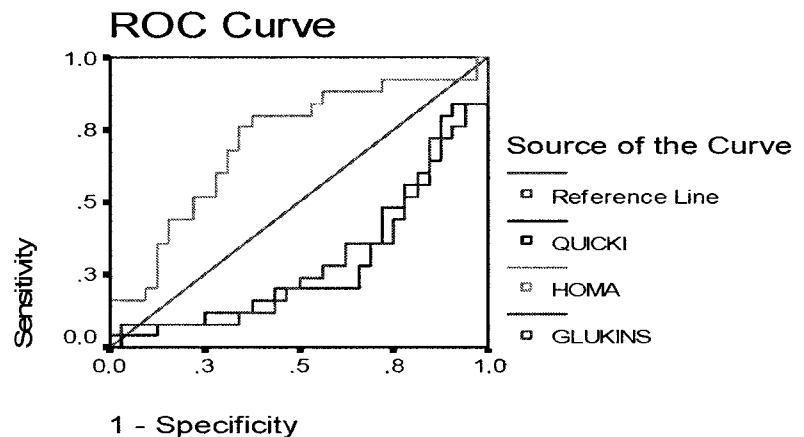


Fig 1. ROC curves for indexes of insulin resistance.

ity in adipose tissues, and suppresses lipolysis both in adipose tissues and in muscles.<sup>23,24</sup>

## CONCLUSIONS

Obesity and type 2 diabetes are globally increasing health problems for young people, with significant individual and public health ramifications with respect to associated morbidity and mortality rates.<sup>1-4</sup> A simpler tool such as HOMA is more appropriate for large epidemiologic studies and is more reliable than FGIR and QUICKI as a measure of insulin resistance among children and adolescents. The use of HOMA is simpler, cheaper, less labor-intensive, less time-consuming, and more acceptable to young people than clamp studies. This study also demonstrates that the HOMA cutoff point for diagnosis of insulin resistance is 3.16 for adolescents. The HOMA cutoff point of >2.5 is valid for adults but not for adolescents. Additional studies are needed to assess the HOMA cutoff point for adolescents.

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