

ORIGINAL ARTICLE

## Improving insulin resistance in obese youth: Choose your measures wisely

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### Abstract

**Objective.** The purpose of this investigation was to compare the homeostasis model assessment of insulin resistance (HOMA-IR) to more direct measures of insulin action before and after lifestyle interventions in obese Latino youth. **Study design.** Eleven obese Latino boys (age  $15.1 \pm 1.6$  years, body mass index (BMI) percentile  $97.3 \pm 3.5\%$ ) and twenty obese Latina girls (age  $14.7 \pm 1.8$  years, BMI percentile  $96.6 \pm 3.6\%$ ) participated in two distinct lifestyle interventions. Boys participated in a 16-week exercise intervention and girls participated in a 12-week nutrition education program. Insulin sensitivity was determined by the frequently sampled intravenous glucose tolerance test (FSIVGTT) in boys and by a 3-hour oral glucose tolerance test with multiple sampling calculations for the whole-body insulin sensitivity index (WBISI) in girls. HOMA-IR was measured for both groups. **Results.** HOMA-IR was correlated at baseline to the FSIVGTT ( $r = -0.57$ ,  $p = 0.07$ ) and the WBISI ( $r = -0.78$ ,  $p < 0.01$ ) and at follow-up (FSIVGTT:  $r = -0.81$ ,  $p = 0.003$ ; WBISI:  $r = -0.71$ ,  $p = 0.001$ ). Post-intervention, insulin sensitivity increased 45% in the boys and 34% in the girls; however, these improvements were not reflected by significant changes in HOMA-IR. **Conclusions.** Improvements in insulin sensitivity following an intervention measured either by the FSIVGTT or an OGTT were not detected by HOMA-IR. Researchers and clinicians should exercise caution in relying on fasting indices, such as HOMA-IR, to determine the impact of lifestyle interventions on insulin sensitivity in overweight youth.

**Key words:** Pediatrics, obesity, type 2 diabetes, exercise, nutrition, Latino

### Introduction

Pediatric obesity has reached epidemic proportions and is a major risk factor for type 2 diabetes (T2D) and the metabolic syndrome (1,2). Insulin resistance plays a central role in the physiological link between obesity and chronic disease risk in children (3). As such, the assessment and treatment of insulin resistance in overweight youth has received much attention in the recent literature (4–6).

The gold-standard for assessing in-vivo insulin resistance is the euglycemic-hyperinsulinemic clamp (7). A second measure commonly employed in pediatric studies is the frequently sampled intravenous

glucose tolerance test (FSIVGTT) (8). Both techniques provide an accurate assessment of whole-body insulin sensitivity but are deemed impractical because they are costly, invasive, and labor intensive. The whole-body insulin sensitivity index (WBISI) derived from an oral glucose tolerance test (OGTT) provides reasonable estimates of insulin sensitivity in overweight youth compared with the euglycemic-hyperinsulinemic clamp ( $r = 0.78$ ,  $P < 0.0005$ ) and the FSIVGTT ( $r = 0.67$ ,  $P < 0.001$ ) (5,6). An OGTT is considered less risky than either the clamp or the FSIVGTT, as there is no infusion of insulin or glucose. However, like both the clamp and FSIVGTT,

an OGTT requires multiple blood draws, which may be limiting in large studies. For practical purposes, surrogate measures of insulin resistance derived from fasting insulin and glucose have been developed (9). The most widely employed measure is the homeostasis model assessment of insulin resistance (HOMA-IR) (10). HOMA-IR is based on a feed-back loop in the basal state between glucose and insulin concentrations, and has been validated extensively against both the clamp and FSIVGTT in a wide range of populations including healthy and overweight children and adolescents (11,12). Most validation studies of HOMA-IR in children have been cross-sectional and no study has evaluated whether HOMA-IR is a reliable measure for changes in insulin sensitivity following interventions in youth.

Therefore, the purpose of this examination was to evaluate whether improvements in insulin sensitivity following lifestyle interventions are equally captured by robust whole-body assessments of insulin action (FSIVGTT or OGTT) and HOMA-IR in overweight insulin resistant youth.

## Research design and methods

The current analysis includes data from two separate interventions in overweight Latino youth. One study employed an exercise strategy and one was a nutritional intervention. Details of the interventions as well as the primary outcomes have been published elsewhere and readers are referred to these publications for further information (13,14). Study designs and participants differed so each is briefly described below. Participants and their parents provided written informed consent and both studies were approved by the Institutional Review Board of the University of Southern California (USC) Health Sciences Campus.

### Participants

*Strength Training Exercise in Adolescent Latinos to Improve Health (STEALTH)*. Eleven Adolescent (Tanner Stage  $\geq 3$ ) Latino Boys with a BMI  $\geq 85^{\text{th}}$  percentile for age and gender completed a twice per week resistance exercise program. The training program was progressive in terms of exercise load and volume, and sessions were monitored throughout by research personal trainers. Prior to the exercise intervention, participants reported to the USC General Clinical Research Center (GCRC) for a comprehensive physical exam, determination of body composition, and assessment of insulin sensitivity via the insulin modified FSIVGTT with minimal modeling.

*Adolescent Latinas Adjusting Sugars (ALAS)*. Twenty Adolescent (Tanner Stage  $\geq 3$ ) Latina girls with a BMI  $\geq 85^{\text{th}}$  percentile for age and gender completed a 12-week nutrition education program, which focused on two specific goals: 1) reduce added sugar consumption to less than 10% of total daily caloric intake; and 2) increase dietary fiber to 14 grams per 1 000 calories. In addition to these goals, general dietary advice was given to encourage a diet where 45–55% of calories were carbohydrate and 30–35% from fat. The program was delivered in weekly 90-minute nutrition education sessions that were taught by trained nutrition educators. Prior to the nutrition program, participants reported to the USC GCRC for a comprehensive physical examination, determination of body composition, and assessment of insulin sensitivity via an OGTT with multiple sampling.

### Common study procedures

All participants underwent a comprehensive physical examination by a paediatrician, which included height, weight, and maturational staging (15). Body composition was determined by a dual-energy x-ray absorptiometry (DEXA) using a Hologic QDR 4500W (Bedford, MA).

### Determination of insulin sensitivity

STEALTH participants reported to the USC GCRC in the afternoon prior to the FSIVGTT. Participants were served a standardized dinner and an evening snack. At ~07.30 h the following day a FSIVGTT was performed. Fasting blood samples were collected in order to determine basal glucose and insulin concentrations. At time zero, glucose (25% dextrose, 0.3 g/kg body weight) was administered intravenously followed 20 minutes later by an insulin injection (0.02 U/kg body weight; Humulin R [regular insulin for human injection; Eli Lilly, Indianapolis, IN]). Blood samples were collected at the following time points: 2, 3, 4, 5, 6, 8, 10, 14, 19, 22, 25, 30, 40, 50, 70, 100, 140, 180, and 210 min. Plasma was analyzed for glucose and insulin, and values were entered into the Minmod Millennium 2003 computer program (version 5.16, Richard N. Bergman, USC) for determination of insulin sensitivity. After the 16-week intervention, participants returned to the USC GCRC to re-assess insulin sensitivity. The follow-up FSIVGTT was performed 48–72 hours after the last exercise bout to minimize any acute effects of exercise on insulin action.

For the ALAS nutrition education program, insulin sensitivity was determined via a 3-hour OGTT. Participants arrived at the USC GCRC following an overnight fast (10–12 hours) and an indwelling

flexible catheter was inserted for blood drawing. Prior to initiating the OGTT, a fasting blood sample was drawn to determine basal glucose and insulin concentrations. A standard glucose dose of 1.75 g/kg up to 75 g was administered orally. Blood samples to determine glucose and insulin concentrations were collected at: 30, 60, 90, 120, 150, and 180 min and were used to quantify the WBISI according to Matsuda and DeFronz (16). The follow-up OGTT was performed within 1 week after the last nutrition education class.

$$\sqrt{\frac{10\,000}{\left(\frac{[\text{fasting glucose} \times \text{fasting insulin}]}{[\text{mean glucose} \times \text{mean insulin}]}\right)}}$$

#### Homeostasis Model Assessment of Insulin Resistance (HOMA-IR)

HOMA-IR was determined according to the computer model described by Levy et al. (17), which can be found at <http://www.dtu.ox.ac.uk/homa/index.php>. Fasting insulin and glucose collected at the time of the FSIVGTT or OGTT were entered into the model.

#### Biochemical assays

Blood samples were centrifuged immediately to obtain plasma and aliquots were frozen at  $-70^{\circ}\text{C}$  until assayed at the USC GCRC Core Laboratory. Glucose was assayed using a Yellow Springs Instruments analyzer, which uses a membrane bound glucose oxidase technique (YSI INC., Yellow Springs, OH; intra-assay CV was 1.0%, inter-assay CV was 2.9%). Insulin was assayed using an automated random access enzyme immunoassay system Tosoh AIA 600 II analyzer (Gibbco Scientific, Inc. Coon Rapids, MN; intra-assay CV was 2.9%, inter-assay CV was 5.6%) using an immunoenzymometric assay method.

#### Statistics

Baseline characteristics of participants were compared by independent sample t-tests. Baseline and follow-up correlations between FSIVGTT or OGTT insulin sensitivity and HOMA-IR measures were examined with Pearson correlation coefficients. Changes in measures of insulin sensitivity/resistance were examined using paired sample t-test. Relationships between changes in FSIVGTT or OGTT insulin sensitivity and HOMA-IR measures were

examined by linear regression. Analyses were performed using SPSS version 15.0 (SPSS Inc., Chicago, IL) with type I error =  $P < 0.05$ . Data are presented as means  $\pm$  standard error of the mean (SEM).

## Results

### Participant characteristics

Descriptive characteristics are presented in Table I. Both groups were obese with no significant differences in fat mass, BMI or BMI percentile. Boys in the exercise intervention had significantly more lean tissue mass compared with females in the nutrition education program, which led to a trend for higher percent fat mass in girls ( $p = 0.07$ ). Age and Tanner Stage were not significantly different between the groups.

### Correlations

HOMA-IR was significantly and inversely associated with the WBISI in girls at baseline ( $r = -0.78$ ,  $p = 0.001$ ) and at follow-up ( $r = -0.71$ ,  $p = 0.001$ ). An inverse association between HOMA-IR and the FSIVGTT in boys was noted at baseline ( $r = -0.57$ ,  $p = 0.07$ ) and follow-up ( $r = -0.81$ ,  $p = 0.003$ ).

### Changes in insulin sensitivity

Both interventions resulted in significant improvements in whole-body measures of insulin sensitivity (Figure 1). On average, the girls in the nutrition education program exhibited a 34% increase in

Table I. Physical characteristics of participants at baseline.

	Boys	Girls
Age (years)	15.1 $\pm$ 1.6	14.7 $\pm$ 1.8
Tanner	4.1 $\pm$ 0.8	4.1 $\pm$ 0.6
Height (cm)	166.3 $\pm$ 10.2*	159.1 $\pm$ 4.8
Weight (kg)	90.0 $\pm$ 18.9	84.0 $\pm$ 20.2
BMI (kg/m <sup>2</sup> )	32.5 $\pm$ 5.3	33.1 $\pm$ 7.3
BMI percentile	97.3 $\pm$ 3.5	96.6 $\pm$ 3.6
Total fat mass (kg)	31.4 $\pm$ 11.3	31.6 $\pm$ 8.2
Total lean mass (kg)	54.5 $\pm$ 10.5*	45.4 $\pm$ 5.8
HOMA-IR	1.9 $\pm$ 1.0	2.4 $\pm$ 1.4
Insulin sensitivity		
• WBISI	-----	3.3 $\pm$ 1.5
• Si-FSIVGTT ( $\times 10^{-4}$ min <sup>-1</sup> /μU/ml)	2.3 $\pm$ 1.0	-----

Data are means  $\pm$  standard deviation. cm = centimeters, kg = kilograms, BMI = Body Mass Index, HOMA-IR = Homeostasis Model Assessment of Insulin Resistance, WBISI = Whole-Body Insulin Sensitivity Index, Si-FSIVGTT = Frequently Sampled Intravenous Glucose Tolerance Test. \* $p < 0.05$ .

the WBISI compared with baseline and boys who participated in the resistance training intervention exhibited a 45% increase over baseline in insulin sensitivity, as measured by the FSIVGTT. In contrast, HOMA-IR measures were not significantly changed compared with baseline in either the girls (11% decrease) or the boys (4% decrease). We further examined whether individual changes in insulin sensitivity, as measured by the WBISI or the FSIVGTT, were related to changes in HOMA-IR in response to the intervention (Figure 2). No clear relationship was observed in boys ( $r^2 = 0.26$ , SEM = 0.42, 95% CI = -0.93–0.11;  $p = 0.11$  for the model) but a significant relationship was observed in girls ( $r^2 = 0.37$ , SEM = 1.59, 95% CI = -1.98–0.43;  $p < 0.01$  for the model).

## Discussion

Our results suggest that HOMA-IR may not detect changes in whole-body insulin sensitivity following interventions in overweight youth. Although HOMA-IR has been shown to be significantly correlated with direct measures of insulin sensitivity in youth, most of these reports have been cross-sectional

in nature (11,12). To our knowledge, this is the first report in children to systematically compare changes in HOMA-IR with more direct measures of insulin resistance following lifestyle interventions.

With the high prevalence of pediatric obesity and associated co-morbidities, a major research emphasis has been placed on interventions to improve insulin resistance (3). By improving insulin resistance, the long-term risk of developing cardiovascular disease and T2D may be decreased. Therefore, the accuracy of assessing the impact of these interventions is important on many levels. In addition to generating sound scientific evidence, children and their families are eager to understand how their participation in clinical studies may have improved their health status. Healthcare practitioners and policy makers are equally interested in understanding how to translate research findings on a wider scale. Although a few intervention studies in overweight youth have employed direct measures of insulin sensitivity (14,18), the majority rely on a fasting index, such as HOMA, to quantify changes in insulin resistance (19–21).

It can be argued that direct measures of insulin sensitivity, such as the clamp or FSIVGTT, are impractical and not always feasible; however, our report shows that employing an OGTT may be a viable alternative. The STOPP-T2D Prevention Study, a large-scale school-based program, established the feasibility of performing OGTTs on over 1 600 middle-school youth (22). Students were asked to fast overnight and then assembled before school or during the first period where the OGTTs were conducted in the school gymnasium. It should be noted that sufficient resources and appropriate supervision are required to conduct OGTTs in a large group setting. We used a 3-hour seven-sample OGTT to estimate insulin sensitivity in our study, however, when the data were analyzed using the more traditional 2-hour five-sample index (fasting, 30, 60, 90, 120 min) the results were virtually identical (data not shown). This suggests that a reduced sampling strategy may be employed to enhance feasibility. When feasible, not only does an OGTT provide a good assessment of insulin sensitivity (6), but it offers the additional benefit of screening for T2D. Incorporating a T2D screening may be particularly relevant in certain populations of overweight youth, such as ethnic minorities, those with a strong family history, or those exposed to hyperglycemia *in utero* (23).

Previous studies in youth have demonstrated improvements in fasting measures of insulin resistance following weight management focused lifestyle interventions (19–21). Unfortunately, more precise comparison measures of insulin resistance were not employed in these investigations and improvements in insulin resistance were not adjusted for changes in

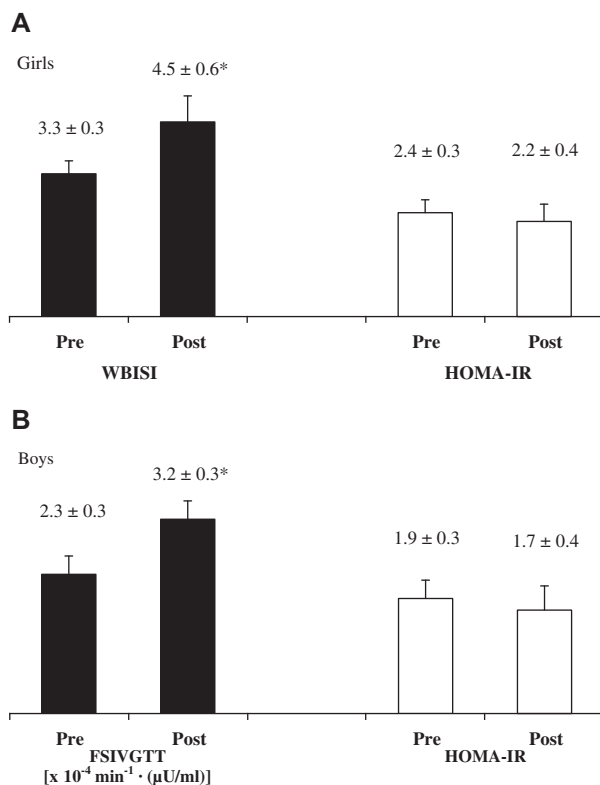


Figure 1. Pre- and post-intervention measures of insulin sensitivity measured by the WBISI and HOMA-IR in girls (A) and the FSIVGTT and HOMA-IR in boys (B). \* $P < 0.05$ .



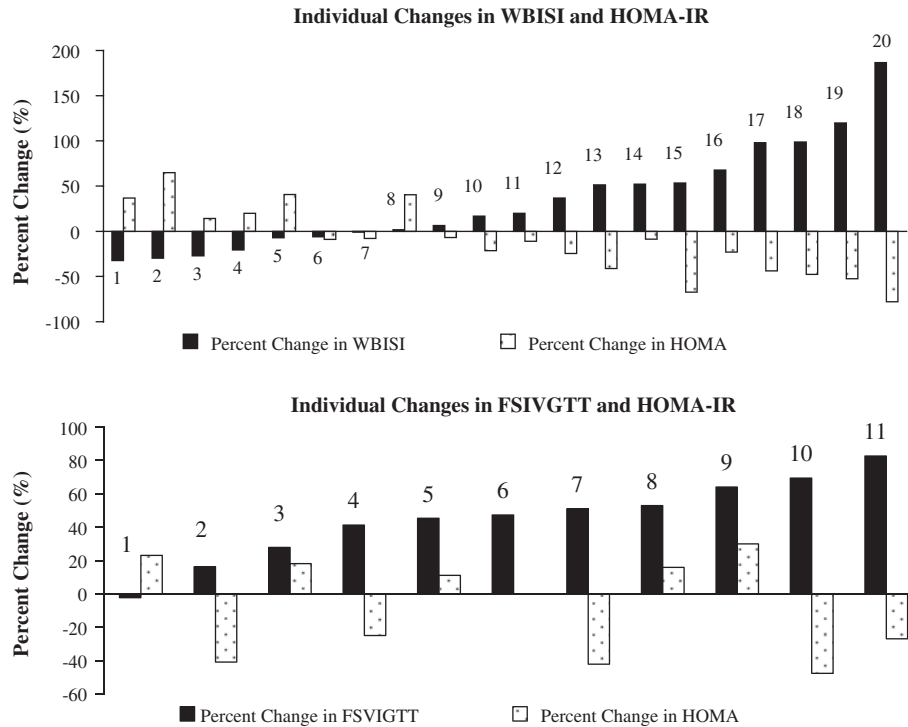


Figure 2. Individual changes in WBISI and HOMA-IR in girls (A) or FSVGTT and HOMA-IR in boys (B) in response to each respective intervention.

body composition. In previous cross-sectional studies of overweight Latino youth, we have shown that once you control for body composition, fasting measures of insulin resistance for example, HOMA-IR, are not significantly associated with FSVGTT derived insulin sensitivity (5). By contrast, 2-hour insulin during an OGTT in addition to indices that reflect post-challenge insulin measures, such as the WBISI, remained associated with insulin sensitivity independent of body composition. Therefore, it is likely that in order to observe improvements in fasting measures of insulin resistance, significant weight/fat loss may be required. In support of this argument, Kelly et al. (24) found that 8-weeks of exercise training in obese youth resulted in significant improvements in cardiorespiratory fitness, endothelial function, and HDL cholesterol but did not significantly change fasting insulin, weight, BMI, or body fat. Had the authors employed a more sensitive assessment of insulin action, they may have observed improvements in this outcome as changes in fitness, endothelial function, and HDL cholesterol could be a reflection of decreased insulin resistance. An alternative explanation for the lack of improvement in HOMA-IR may be related to our population. Other than meeting BMI criteria, very few youth from the two studies met the criteria for the metabolic syndrome or pre-diabetes at baseline. Therefore, our

findings may not be generalizable to all obese youth. HOMA-IR may prove to be a more sensitive measure in obese youth with abnormal clinical levels of obesity-related metabolic risk factors.

HOMA-IR is thought to be a reflection of hepatic rather than peripheral insulin resistance (25). At high levels of body fat i.e., obesity, an increased delivery of free fatty acids from the adipose tissue to the liver promotes hepatic insulin resistance and hyperinsulinemia (26). If an intervention results in decreases in adiposity, it is likely that decreases in fasting insulin will also be observed. It remains unclear the extent to which changes in peripheral versus hepatic insulin resistance differentially impact obesity-related disease (27). The interventions described in the present investigation were designed to improve insulin sensitivity as more proximal measures of T2D risk rather than promote weight or fat loss from an energy balance perspective. In this regard, neither fat mass nor weight were significantly reduced in either intervention (Exercise fat mass change =  $-1.3 \pm 2.9$  kg,  $p = 0.15$ ; weight change =  $1.9 \pm 3.5$  kg,  $p = 0.11$  and Nutrition fat mass change =  $-0.8 \pm 2.1$  kg,  $p = 0.18$ ; weight change =  $0.9 \pm 3.1$  kg,  $p = 0.30$ ). However, weight change was significantly associated with change in HOMA-IR ( $r = 0.35$ ,  $p = 0.05$  for pooled study samples) suggesting that those youth who lost the most weight

may have improved hepatic insulin sensitivity the most. Longer studies are needed to determine whether short-term improvements in insulin resistance equate to decreases in T2D in this population. Nonetheless, our findings underscore the importance of including comprehensive measures of disease risk in future studies.

The strengths of our study include a relatively homogeneous sample of participants in terms of ethnicity, adiposity, and pubertal status. We examined an exercise as well as nutritional intervention and each was gender specific. It can be argued that from a practical perspective this design is not readily translatable to the clinical setting where various ethnicities, genders and age groups are often enrolled in more comprehensive lifestyle programs. However, given the fact that the correlations between HOMA-IR and directly measured insulin resistance vary by age, gender, and obesity in youth (28), our design minimizes variability related to these factors on the outcome of insulin resistance. Lastly, our comparison measures of insulin resistance included an extended OGTT with multiple sampling and the FSIVGTT, which themselves have limitations compared with the gold-standard euglycemic-hyperinsulinemic clamp technique.

It is of interest to note that we did observe significant correlations between HOMA-IR and both the FSIVGTT and the WBISI measures, at baseline and follow-up. Although baseline correlations in boys did not reach the level of significance ( $p = 0.07$ ), we believe it was a result of the limited power due to the small sample size. When we increased the sample size to 27 by including boys from the control arm of the intervention and those that did not complete follow-up testing, we did observe a significant inverse association ( $r = -0.45$ ,  $p = 0.02$ ; see supplemental Figure). We also noted that changes in the WBISI were related to changes in HOMA-IR in the girls even though HOMA-IR did not significantly change. This may be an indication that HOMA-IR is not sensitive enough to capture changes of insulin action. It is also not altogether surprising given that fasting insulin is a key component in the calculation of both HOMA-IR and the WBISI.

In summary, HOMA-IR does not similarly reflect improvements in insulin resistance following lifestyle interventions compared with either the FSIVGTT or the WBISI. These findings suggest that more robust measures of insulin resistance should be employed in studies examining the impact of interventions on obesity-related disease risk. Ultimately, testing the effects of various interventions in a comprehensive manner will have the greatest potential to impact the health and well-being of the population.

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**Declaration of interest:** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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### Supplementary material available online

Supplementary Figure 1.