

Association Between Insulin Sensitivity and Post-Glucose Challenge Plasma Insulin Values in Overweight Latino Youth

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OBJECTIVE — To determine associations between directly measured insulin sensitivity (SI) and oral glucose tolerance test (OGTT)-derived plasma insulin values, or calculated SI indices, in overweight peripubertal Latino children at risk for type 2 diabetes.

RESEARCH DESIGN AND METHODS — Thirty overweight Latino children with a family history of type 2 diabetes, aged 8–13 years, Tanner stages 1–2, underwent an OGTT. Fasting and 2-h plasma insulin values and OGTT-derived SI indices were compared with SI derived from a frequently sampled intravenous glucose tolerance test (FSIGTT) with minimal model analysis, before and after adjustment for total body fat and lean tissue mass, or BMI.

RESULTS — FSIGTT-derived SI for all subjects was $1.62 \pm 0.78 \times 10^{-4} \text{ min}^{-1} \cdot (\mu\text{U/ml})$, with no sex differences. SI correlated (all P values < 0.001) with fasting ($r = -0.57$) and 2-h ($r = -0.58$) plasma insulin and all SI indices ($r = -0.57$ to 0.67). After adjusting for total body fat and lean tissue mass, or BMI, the associations between SI and either fasting insulin or fasting SI indices were no longer significant. However, the 2-h insulin and post-glucose challenge SI indices maintained significant independent associations with SI, even after adjustment for body composition.

CONCLUSIONS — In overweight, peripubertal Latino children at risk for type 2 diabetes, the 2-h plasma insulin value and postchallenge SI indices are better independent correlates of SI than fasting values, after accounting for body composition. The 2-h insulin may therefore be superior to fasting insulin as a single blood sample value for clinical or epidemiological estimates of SI, especially when combined with assessment of body composition.

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The pathogenesis of type 2 diabetes in adults is characterized by the combination of decreased insulin sensitivity (SI) and diminished β -cell insulin secretion (1). The two methods tradition-

ally used to measure SI, the euglycemic-hyperinsulinemic clamp (2) and the frequently sampled intravenous glucose tolerance test (FSIGTT) with minimal model analysis (3), are costly labor- and

time-intensive research tools that do not lend themselves to use in clinical or epidemiological settings.

Thus, there have been attempts to find easier ways to estimate SI in adults at risk for type 2 diabetes. For example, directly measured SI correlates well with fasting insulin, homeostasis model assessment for insulin resistance index (HOMA-IRI), and other calculated SI indices based on insulin and glucose levels obtained during an oral glucose tolerance test (OGTT) (4–7). Significantly, these simpler SI indices are predictive of progression to type 2 diabetes in these adult populations (8,9).

In children and adolescents there has been an alarming increase in the incidence of type 2 diabetes in recent years, particularly among overweight pubertal youth and in high-risk ethnic populations (10,11). However, the natural history of changes in SI and β -cell insulin secretion during adolescence, which would predict progression to type 2 diabetes during adolescence, remains largely unknown, and it is difficult to predict the onset of type 2 diabetes by measuring such changes. Studies of SI in the pediatric population have utilized either the hyperinsulinemic-euglycemic clamp (12–14) or the FSIGTT/minimal model approach (15–18). However, no studies to date have directly compared SI measured by FSIGTT with estimates of SI derived from OGTT insulin values in a pediatric population at high risk for type 2 diabetes.

Therefore, the purpose of this study was to determine whether OGTT-derived plasma insulin values and SI indices in peripubertal overweight Latino adolescents compare reliably with SI derived from the FSIGTT and whether such associations are independent of differences in body composition.

RESEARCH DESIGN AND METHODS

Subjects

Thirty children (19 boys and 11 girls) were recruited through clinics and word-

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Abbreviations: AUC-insulin, area under the insulin curve; CDC, Centers for Disease Control and Prevention; FSIGTT, frequently sampled intravenous glucose tolerance test; GCRC, USC General Clinical Research Center; HOMA-IRI, homeostasis model assessment for insulin resistance index; IGT, impaired glucose tolerant; NGT, normal glucose tolerant; OGTT, oral glucose tolerance test; SI, insulin sensitivity; WBISI, whole-body SI index.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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of-mouth based on the following criteria: 1) age 8–13 years; 2) BMI >85th percentile for age and sex per Centers for Disease Control and Prevention (CDC) standards; 3) Latino ancestry (all four grandparents Latino); and 4) family history of type 2 diabetes in a parent, sibling, or grandparent. Children were pubertal stage Tanner 1 (five boys, one girl) or Tanner 2 (14 boys and 10 girls) and were predominantly of Mexican-American heritage. Children were excluded if they had prior major illness; took medications or had a condition known to influence body composition, insulin action, or insulin secretion (e.g., glucocorticoid therapy, hypothyroidism); or were diagnosed with diabetes by OGTT (19). This study was approved by the Institutional Review Board, Health Science Campus, University of Southern California. Informed consent and child assent were obtained from all parents and children.

Protocol design

Outpatient visit: OGTT. Children arrived at the University of Southern California General Clinical Research Center (GCRC) at ~8:00 A.M. after an overnight fast. A topical anesthetic (EMLA cream; Aztrozeneca LP, Wilmington, DE) was applied to the antecubital area of one arm, and at ~9:00 A.M., a flexible intravenous catheter was placed in an antecubital vein. Subjects ingested 1.75 g oral glucose solution/kg body wt (to maximum 75 g) at “time 0.” Blood was sampled and assayed for glucose and insulin at times –5 (“fasting”), 15, 30, 45, 60, and 120 min (“2-h”). Glucose values from the OGTT demonstrated that 25 subjects had normal glucose tolerance, 5 subjects (3 boys and 2 girls) had impaired glucose tolerance, and none had diabetes (19).

The following SI indices based on OGTT plasma glucose and insulin values were calculated: HOMA-IRI (5) [$\text{HOMA-IRI} = \text{fasting insulin } (\mu\text{U/ml}) \times \text{fasting glucose } (\text{mmol/l}) / 22.5$], ratios of insulin/glucose at fasting and 2-h time points, area under the insulin curve (AUC-insulin) (20), and the whole-body SI index (WBISI) (7) [$\text{WBISI} = 10,000 / \text{square root of } (\text{fasting glucose} \times \text{fasting insulin}) \times (\text{mean OGTT glucose} \times \text{mean OGTT insulin})$].

Inpatient visit

Children were admitted to the GCRC in the afternoon an average of 8 days (range

5–18 days) following the OGTT. A whole-body dual-energy X-ray absorptiometry scan was performed to determine total body fat and lean tissue mass using a Hologic QDR 4500W (Hologic, Bedford, MA). The children were served dinner and an evening snack, with only water permitted after 8:00 P.M.

FSIGTT commenced the following morning. At 6:30 A.M. EMLA was applied, followed ~1 h later by flexible intravenous catheter placement in bilateral antecubital veins. Two fasting blood samples were drawn at –15 and –5 min for determination of basal glucose and insulin. At time 0, glucose (25% dextrose, 0.3 g/kg body wt) was administered intravenously. Blood samples were collected at 2, 3, 4, 5, 6, 8, 10, 14, 19, 22, 25, 30, 40, 50, 70, 100, 140, 180, and 210 min. Insulin (0.02 units/kg body wt; Humulin R [regular insulin for human injection]; Eli Lilly, Indianapolis, IN) was injected intravenously at 20 min. Plasma was analyzed for glucose and insulin, and values were entered into the Minmod Millennium 2002 computer program (version 5.7, Richard N. Bergman) for determination of SI (21). The validity of FSIGTT-derived SI compared with the euglycemic-hyperinsulinemic clamp has been directly established in adults (22). While a direct comparison of the two techniques has not been reported in children, indirect validation of FSIGTT-determined SI in children and adolescents comes from the demonstration of insulin resistance in obese or pubertal children known to be insulin resistant using clamp techniques (15,16).

Measures and assays

Height and weight were recorded at each visit, and the average of the two measurements was used for analysis. BMI and BMI percentiles for age were determined based on established CDC normative curves using computer software EpiInfo 2000, version 1.1. Glucose was assayed using a Yellow Springs Instrument 2700 Analyzer (YSI, Yellow Springs, OH). Insulin was assayed using an enzyme-linked immunosorbent assay kit from Alpco (Wyndham, NH), with 0% cross-reactivity for intact human proinsulin, <0.5% for proinsulin des (31–32) and proinsulin split (32–33), 98% for proinsulin des (64–65), and 56% for proinsulin split (65–66).

Statistical analysis

Sex differences in physical and metabolic characteristics were examined using the independent Student's *t* test following log transformation of variables that were not normally distributed (weight, total fat mass, BMI, insulin, and SI indices). Spearman correlation analysis was used to establish associations between SI, body composition measures, and individual non-log-transformed insulin values and SI indices. Multivariate linear regression analysis was used to establish the independent contribution of OGTT-derived insulin values and SI indices to FSIGTT-derived SI after adjustment for total body fat and lean tissue mass, or BMI. For these analyses the dependent variable was SI, and the independent variables were fasting insulin, 2-h insulin, HOMA-IRI, insulin/glucose ratios at fasting and 2-h, AUC-insulin, and WBISI. Total body fat mass and total body lean tissue mass, or BMI, were entered as covariates in addition to age and sex. All analyses were performed using SPSS version 9.0 (SPSS, Chicago, IL), with a type I error set at $P < 0.05$.

RESULTS

Physical and metabolic characteristics of study subjects

There were no significant sex differences in body composition measures, SI, 2-h glucose, fasting or 2-h insulin, or SI indices (Table 1). Fasting glucose was slightly lower in girls. Data for boys and girls were combined for the remaining analyses.

Correlations between FSIGTT-derived SI, OGTT-derived insulin and SI indices, and body composition measures

SI correlated significantly with fasting and 2-h insulin and all SI indices (Table 2). Fasting insulin, HOMA-IRI, and fasting insulin/glucose correlated with both fat mass and BMI. The 2-h insulin, 2-h insulin/glucose, and AUC-insulin levels did not correlate with either fat mass or BMI. WBISI did not correlate significantly with BMI and correlated less strongly with fat mass. There was no significant correlation between SI and plasma glucose at any OGTT time point (results not shown). As expected, BMI correlated very strongly with total body fat mass.

Table 1—Physical and metabolic characteristics of subjects

	Boys	Girls	Total
n	19	11	30
Age (years)	10.4 ± 0.4	10.0 ± 0.5	10.3 ± 0.3
Weight (kg)	56.4 ± 3.5	53.7 ± 4.1	55.4 ± 2.7
Height (cm)	143.9 ± 2.2	140.7 ± 2.8	142.7 ± 1.7
BMI (kg/m ²)	26.8 ± 1.1	26.8 ± 1.1	26.8 ± 0.8
BMI percentile (%)	97.3 ± 0.7	98.2 ± 0.4	97.6 ± 0.5
Total body fat mass (kg)	21.6 ± 1.9	22.3 ± 2.3	21.8 ± 1.4
Total body lean tissue mass (kg)	32.4 ± 1.7	29.4 ± 2.0	31.3 ± 1.3
SI [$\times 10^{-4} \text{ min}^{-1} \cdot (\mu\text{U/ml})$]	1.59 ± 0.18	1.66 ± 0.25	1.62 ± 0.14
Fasting glucose (mg/dl)	91.5 ± 1.1	87.4 ± 1.3*	90.0 ± 0.9
2-h glucose (mg/dl)	124.0 ± 3.1	117.2 ± 5.8	121.5 ± 2.9
Fasting insulin ($\mu\text{U/ml}$)	28.7 ± 4.4	20.0 ± 2.1	25.5 ± 2.9
2-h insulin ($\mu\text{U/ml}$)	202.4 ± 41.0	193.0 ± 40.9	199.0 ± 29.6
HOMA-IRI	6.53 ± 1.02	4.33 ± 0.48	5.73 ± 0.69
Fasting insulin/glucose ($\mu\text{U} \cdot \text{ml}^{-1} \cdot \text{mg}^{-1} \cdot \text{dl}^{-1}$)	0.31 ± 0.05	0.23 ± 0.02	0.28 ± 0.03
2-h insulin/glucose ($\mu\text{U} \cdot \text{ml}^{-1} \cdot \text{mg}^{-1} \cdot \text{dl}^{-1}$)	1.56 ± 0.28	1.55 ± 0.28	1.56 ± 0.20
AUC-insulin ($\mu\text{U} \cdot \text{ml}^{-1} \cdot 2 \text{ h}^{-1}$)	433.4 ± 60.7	404.9 ± 61.0	423.0 ± 43.9
WBISI	1.94 ± 0.30	1.96 ± 0.24	1.95 ± 0.21

Data are means ± SE. * $P < 0.05$

Multivariate linear regression analysis to assess the independent contributions of body composition, OGTT-derived insulin values, and SI indices on FSIGTT-derived SI (Table 3)

Results from the multivariate regression analysis indicated that total body fat mass (after adjustment for total body lean tissue mass, age, and sex) had a significant negative relationship with SI (model 1). The associations between SI and fasting insulin (model 2) and HOMA-IRI (model 3) were no longer significant after adjusting for total body fat. In contrast, the 2-h insulin (model 4) and AUC-insulin (model

5) remained significantly associated to SI after correction for body fat. Thus, 2-h insulin and AUC-insulin added 14 and 23%, respectively, to the variability in SI above that predicted by body fat alone. Similar analyses demonstrated that 2-h insulin/glucose (model $R^2 = 0.65$, $P = 0.003$) and WBISI (model $R^2 = 0.70$, $P = 0.001$) remained significantly associated with SI, whereas fasting insulin/glucose did not (results not shown in table). Adjusting the above models for Tanner stage did not affect the analyses.

Multivariate regression analysis was also performed using BMI as the independent variable for body composition in

place of total body fat mass and lean tissue mass, again adjusted for age and sex, showing a model $R^2 = 0.46$, $P = 0.044$. There was no significant association between SI and either fasting insulin (model $R^2 = 0.50$) or HOMA-IRI (model $R^2 = 0.49$) when these independent variables were added to the regression. However, the associations between SI and both the 2-h insulin (model $R^2 = 0.60$, $P = 0.007$) and AUC-insulin (model $R^2 = 0.64$, $P = 0.002$) remained significant after adjustment for BMI.

CONCLUSIONS— The primary purpose of this study was to determine the extent to which directly measured SI compares to plasma insulin levels and calculated SI indices obtained from an OGTT in a pediatric population at risk for developing type 2 diabetes. Our major results indicate that although all OGTT-derived insulin values and indices correlate with directly determined SI, only the 2-h insulin level and those SI indices that emphasize postchallenge insulin levels (AUC-insulin, 2-h insulin/glucose, and WBISI) maintain a significant association with SI once body composition has been accounted for. Put another way, in the population of Latino adolescents in this study, fasting insulin and indices derived from fasting blood samples appear to have no independent relationship with SI beyond that reflected in body composition. In contrast, the relationship between postchallenge insulin values and SI do persist independently of body fatness.

The current study is the first to directly compare OGTT-derived SI indices with direct measurement of SI in children. Of the indices we evaluated, the AUC-insulin and WBISI had the strongest direct correlation with SI and remained significantly associated after correction for body fat and lean tissue mass or BMI. However, because these indices rely on multiple blood samples following glucose challenge, they remain problematic in the clinical or epidemiological setting. The ideal in these settings would be a single blood sample value or index that relates strongly to SI independent of other clinically obtainable measures.

Historically, the single blood sample values most commonly used to reflect SI have been fasting insulin and fasting SI indices. The most frequently reported fasting index, HOMA-IRI, correlates

Table 2—Spearman correlation between FSIGTT-derived SI, OGTT-derived insulin values and SI indices, and measures of body composition

	SI	Total body fat mass	BMI
SI	—	−0.64*	−0.49†
Total body fat mass	−0.64*	—	0.92*
BMI	−0.49†	0.92*	—
Fasting insulin	−0.57*	0.54†	0.47†
2-h insulin	−0.58*	0.17	0.08
HOMA-IRI	−0.57*	0.55†	0.47†
Fasting insulin/glucose	−0.59*	0.54†	0.47†
2-h insulin/glucose	−0.61*	0.22	0.14
AUC-insulin	−0.65*	0.21	0.14
WBISI	0.67*	−0.37‡	−0.28

* $P < 0.001$; † $P < 0.01$; ‡ $P < 0.05$.

Table 3—Multivariate regression analysis to examine the contribution of insulin measures on insulin sensitivity after adjustment for total body fat and lean tissue mass

	Parameter estimate \pm SEE	P
Model 1 ($R^2 = 0.49$)		
Sex	0.14 \pm 0.26	NS
Age	−0.20 \pm 0.12	NS
Total body fat mass	−0.061 \pm 0.029	0.04
Total body lean mass	0.031 \pm 0.044	NS
Model 2 ($R^2 = 0.56$)		
Sex	0.07 \pm 0.25	NS
Age	−0.21 \pm 0.12	NS
Total body fat mass	−0.061 \pm 0.027	0.04
Total body lean mass	0.066 \pm 0.046	NS
Fasting insulin	−0.020 \pm 0.011	NS
Model 3 ($R^2 = 0.55$)		
Sex	0.06 \pm 0.25	NS
Age	−0.22 \pm 0.12	NS
Total body fat mass	−0.060 \pm 0.028	0.04
Total body lean mass	0.066 \pm 0.047	NS
HOMA-IRI	−0.081 \pm 0.047	NS
Model 4 ($R^2 = 0.63$)		
Sex	0.15 \pm 0.23	NS
Age	−0.21 \pm 0.11	NS
Total body fat mass	−0.058 \pm 0.025	0.03
Total body lean mass	0.041 \pm 0.038	NS
2-h insulin	−0.0019 \pm 0.0006	0.006
Model 5 ($R^2 = 0.72$)		
Sex	0.20 \pm 0.20	NS
Age	−0.22 \pm 0.10	0.03
Total body fat mass	−0.071 \pm 0.022	0.004
Total body lean mass	0.066 \pm 0.034	NS
AUC-insulin	0.00003 \pm 0.00001	<0.001

Dependent variable = insulin sensitivity by minimal model.

strongly with fasting insulin alone, from which it is directly derived (9) and does predict progression to diabetes in adult populations at risk. In an earlier report (23) from a nonobese, multiethnic childhood cohort, we found that while HOMA-IRI did predict SI, it offered no predictive benefit beyond fasting insulin alone. Both fasting insulin and HOMA-IRI, as well as fasting insulin/glucose, correlate with direct measures of SI in normal glucose tolerant (NGT), impaired glucose tolerant (IGT), and type 2 diabetic adult populations. (4,5,24–27) Likewise, in obese children and adolescents, HOMA-IRI correlates with clamp-derived SI (28). However, in none of these prior studies were the associations between SI and fasting SI indices adjusted for body composition.

As in the above studies, our current results demonstrate that fasting insulin, HOMA-IRI, and fasting insulin/glucose correlate to a similar degree with FSIGTT-

derived SI. Importantly, however, these relationships were not maintained once correction was made for body fat and lean tissue mass or BMI. This stands in contrast to our previous report (23), where fasting insulin did predict SI independent of body weight. This is likely due to the smaller numbers and more homogenous sample with respect to body fat in the current study population. In addition, the fasting insulin used in our prior report was obtained on the same day that the FSIGTT was performed, thus yielding stronger relationships to SI and potentially accounting for the differences seen in the regression analyses in our earlier report compared with the current findings.

In contrast to fasting insulin and indices, the associations between SI and the 2-h insulin, as well as the postchallenge SI indices, were maintained even after correction for body composition. The reason for this finding is unclear. It may be that

hepatic insulin resistance, the primary determinant of fasting insulin levels, is more closely related to adiposity than peripheral insulin resistance. Peripheral insulin resistance is the primary defect in SI in the pubertal age group (13), and post-glucose challenge glucose disposal largely occurs in the periphery (29). The 2-h insulin value may thus be more sensitive in reflecting this peripheral resistance than fasting insulin and hence shows stronger associations with whole-body SI as determined by the FSIGTT.

Since the degree of rise in plasma insulin post-glucose challenge in insulin-resistant subjects is dependent on adequate β -cell compensatory secretion (30), the usefulness of the 2-h insulin for estimating SI will likely depend on the glucose tolerance status of the subject. In NGT subjects, where insulin secretion is preserved, there is a strong correlation between SI and postchallenge insulin values, including the 2-h value (4,27,31–33). The correlation between postchallenge insulin and SI may be weaker in IGT subjects (4,31,33), although it may still be useful in those with preserved insulin secretion (34). Our study lacks a sufficient number of subjects with IGT to adequately address this question. Finally, the 2-h insulin does not correlate as well with SI as the fasting insulin in type 2 diabetes, where β -cell secretory capacity is clearly compromised (4).

Taken as a whole, our results suggest that in Latino children at risk for diabetes who have NGT, or possibly IGT with normal insulin secretory capacity, 2-h insulin might be a better independent predictor of SI than fasting insulin or fasting indices. Support for this idea comes from Stumvoll et al. (35), who reported that the 2-h insulin, along with BMI and OGTT 90-min glucose, are the best independent predictors of clamp-derived SI in a Caucasian adult population with NGT. If, as in adults, decreased SI and IGT prove to be predictive of which children progress to overt type 2 diabetes, it may be reasonable to use a single 2-h postchallenge blood sample for both glucose and insulin as a diagnostic screening tool.

Screening children for diabetes using 2-h samples, rather than the currently recommended fasting samples (36), would clearly complicate the screening process and needs to be weighed against the benefits of the increased information gleaned from such an approach. A 2-h

glucose would differentiate diabetes from IGT and NGT, while a 2-h insulin would provide an estimate of SI in NGT, and possibly IGT, children. Since 2-h insulin has a stronger independent association with SI than fasting insulin or HOMA-IRI, it may be more useful in epidemiological prediction models attempting to identify the children at highest risk for type 2 diabetes, particularly when combined with measures of body composition. This possibility is supported by the finding that the 2-h insulin, independently of BMI, does indeed predict deterioration from NGT to either IGT or diabetes in an adult population at significant risk for type 2 diabetes (37). At this time we are not prepared to recommend switching to a post-challenge screening methodology on a routine basis. Further studies with more subjects spanning the range of puberty will be necessary to fully evaluate the value of the 2-h versus fasting sample in predicting SI and the development of type 2 diabetes.

The current study is limited by the relatively small study population and the fact that it does not include adolescents across the spectrum of pubertal stages. However, our population does correspond closely with the recommended timing for diabetes screening in children at risk for type 2 diabetes (36). It will be important to determine if the independent relationship between SI and 2-h insulin is maintained in a larger number of subjects across all pubertal stages. It will also be important to determine if this relationship tracks longitudinally, which could make it particularly useful as a clinical marker of SI in individual patients. Another limitation of this study is the homogenous ethnic background of our study subjects, making it difficult to generalize the results to the entire population of overweight youth. However, insofar as overweight Latino youth with a family history of type 2 diabetes represent a population at particular high risk, characterization of their metabolic risk factors, including SI, may be critical to establish the natural history of IGT and type 2 diabetes in adolescents. This is the necessary first step to developing targeted interventions to prevent type 2 diabetes in at-risk populations of youth.

In summary, we found the postchallenge 2-h insulin value to be a stronger independent correlate of SI than fasting insulin or fasting SI indices in this popu-

lation of overweight Latino children. The utility of the 2-h insulin as a clinical or epidemiological indicator of SI may be limited primarily to those children with NGT. Future studies should determine whether the 2-h insulin value can serve as an indicator of SI across the spectrum of pubertal development and in children with IGT, and whether this value could ultimately be useful in predicting progression to type 2 diabetes in this population, especially when combined with body composition assessment. If indeed it turns out to have predictive value, a single 2-h blood sample measuring glucose and insulin may ultimately be the preferred method to screen appropriate childhood candidates for diabetes prevention efforts.

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