Measuring β-Cell Function Relative to Insulin Sensitivity in Youth

Does the hyperglycemic clamp suffice?

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OBJECTIVE—To compare β-cell function relative to insulin sensitivity, disposition index (DI), calculated from two clamps (2cDI, insulin sensitivity from the hyperinsulinemic-euglycemic clamp and first-phase insulin from the hyperglycemic clamp) with the DI calculated from the hyperglycemic clamp alone (hcDI).

RESEARCH DESIGN AND METHODS—Complete data from hyperglycemic and hyperinsulinemic-euglycemic clamps were available for 330 youth: 73 normal weight, 168 obese with normal glucose tolerance, 57 obese with impaired glucose tolerance, and 32 obese with type 2 diabetes. The correlation between hcDI and 2cDI and Bland-Altman analysis of agreement between the two were examined.

RESULTS—Insulin sensitivity and first-phase insulin from hcDI showed a hyperbolic relationship. The hcDI correlated significantly with 2cDI in the groups combined ($r = 0.85$, $P < 0.001$) and within each group separately ($r \geq 62$, $P < 0.001$). Similar to 2cDI, hcDI showed a declining pattern of β-cell function across the glucose-tolerance groups. Overall, hcDI values were 27% greater than 2cDI, due to the hyperglycemic versus euglycemic conditions, reflected in a positive bias with Bland-Altman analysis.

CONCLUSIONS—β-Cell function relative to insulin sensitivity could be accurately evaluated from a single hyperglycemic clamp, obviating the need for two separate clamp experiments, when lessening participant burden and reducing research costs are important considerations.

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The high prevalence of obesity and its associated comorbidity of glucose dysregulation in youth have increased the need for methods of assessing glucose-insulin dynamics in pediatric research (1,2). Insulin sensitivity and insulin secretion are impaired in obesity-associated dysglycemia (3,4). Insulin secretion is coupled to insulin sensitivity through a hyperbolic relationship; hence, insulin secretion is expressed relative to insulin sensitivity (i.e., the disposition index [DI]), to accurately assess β-cell function (5–7). When the clamp technique is used, which is accepted as the gold standard for the assessment of insulin sensitivity and secretion, the measurement of DI requires a hyperglycemic clamp to measure first-phase insulin and a hyperinsulinemic-euglycemic clamp, on a separate occasion, to measure insulin sensitivity (2). Owing to this need for two separate clamp experiments, measuring DI using the clamp methodology imposes significant participant burden in adults and children, but more so in the latter, and increases research costs, especially when repeated measurements are needed over time in longitudinal trials. Conversely, DI was first described and is commonly calculated from the frequently sampled intravenous glucose tolerance test (FSIVGTT), in which insulin sensitivity and acute insulin release are both measured from a single experiment (5,6,8). Mathematical modeling of DI (9,10), in addition to simple estimates of DI from the oral glucose tolerance test (OGTT) (11–13), has also been described. In the current study, we aimed to examine if DI calculated from a single hyperglycemic clamp, delivering both measures of insulin sensitivity and first-phase insulin, could provide an adequate measure of β-cell function relative to insulin sensitivity compared with DI derived from two clamps, a hyperinsulinemic-euglycemic clamp for insulin sensitivity and a hyperglycemic clamp for first-phase insulin secretion (2,14,15).

RESEARCH DESIGN AND METHODS

Complete data from a hyperinsulinemic-euglycemic clamp and a synchronized hyperglycemic clamp were available for 330 youth (146 African American, 178 Caucasian, 6 biracial; aged 8 to <20 years) as participants in the National Institutes of Health-funded studies "Childhood Metabolic Markers of Adult Morbidity in Blacks" and "Childhood Insulin Resistance" (4,16,17). All procedures were approved by the University of Pittsburgh Institutional Review Board, and consent and assent was obtained before any procedure.

Participants were divided into four categories: 73 normal weight (NW; BMI 5th to <85th percentile), 168 overweight/obese (BMI ≥85th percentile) with normal glucose tolerance (OB-NGT), 57 overweight/obese with impaired glucose tolerance (OB-IGT), and 32 overweight/obese with a diagnosis of type 2 diabetes and negative pancreatic auto-antibodies (OB-T2DM). Treatments for participants with type 2 diabetes were 22% lifestyle therapy alone, 47% metformin alone, 9% insulin alone, and 22% metformin and insulin combined. Glycated hemoglobin (HbA_{1c}) above 8.5% was an exclusion criterion for subjects with diabetes for patient safety reasons in undergoing clamp studies (17,18).

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Experimental procedures

Each clamp study was conducted after a 10–12-h overnight fast after admission the prior afternoon to the Pediatric Clinical and Translational Research Center at Children's Hospital of Pittsburgh of UPMC. All experimental procedures for the hyperinsulinemic-euglycemic clamp (12,17–20) and the hyperglycemic clamp (12,17,18,20) have been described in detail. Metformin and long- and intermediate-acting insulin use was discontinued in participants with diabetes 48 h before either clamp (17).

Briefly, a 3-h hyperinsulinemic (40 mU/m^2/min in NW and 80 mU/m^2/min in overweight/obese for suppression of hepatic glucose production)-euglycemic (100 mg/dL) clamp was performed after a 10–12 h overnight fast (4,21). Plasma glucose was clamped at 100 mg/dL (5.5 mmol/L) by a variable rate infusion of 20% dextrose in water, and arterialized blood samples for glucose and insulin determinations were collected from a heated hand vein. On a separate occasion, 1 to 4 weeks apart, a 2-h hyperglycemic clamp (~225 mg/dL) was performed in random order as before (2,4,22). Plasma glucose concentration was rapidly increased to ~225 mg/dL with a bolus dextrose infusion and maintained at 225 mg/dL with a variable-rate infusion of 20% dextrose in water for 2 hours. In overweight/obese participants without diabetes, glucose tolerance status was determined with HbA_{1c} and/or a 2-h OGTT (23–25). Dual-energy X-ray absorptiometry was used to assess body composition (3,4,16–18).

Biochemical analyses

Plasma glucose was measured by the glucose oxidase method (Yellow Springs Instrument Co., Yellow Springs, OH). Plasma insulin was analyzed by a commercial radioimmunoassay (catalog no. 1011; LINCO Research, St. Charles, MO) (4).

Calculations

Peripheral insulin sensitivity from the hyperinsulinemic-euglycemic clamp (IS_{Eu}) was calculated during the last 30 min (150–180) to be equal to the rate of exogenous glucose infusion divided by the steady-state clamp insulin concentration multiplied by 100 and expressed per kg body weight (mg/kg/min per μU/mL) (4,17). Insulin sensitivity from the hyperglycemic clamp (IS_{Hyp}) was calculated during the last 60 min (60–120) of the clamp as the mean exogenous glucose infusion minus urinary glucose excretion, divided by the mean insulin concentration of five determinations during the same time period. First-phase insulin (μU/mL) was calculated as the mean insulin concentration of five measurements at 2.5, 5, 7.5, 10, and 12.5 min during the hyperglycemic clamp (26,27). β-Cell function relative to insulin sensitivity, the DI (mg/kg/min), was calculated as the product of insulin sensitivity (IS_{Eu} or IS_{Hyp}) and first-phase insulin based on a hyperbolic relationship as before (4,17). Specifically, the DI from the combination of both clamps (2cDI, mg/kg/min) was calculated as the product of first-phase insulin from the hyperglycemic clamp and IS_{Eu} (4,17), whereas the DI from the hyperglycemic clamp alone (hcDI, mg/kg/min) was calculated as the product of first-phase insulin and IS_{Hyp}.

Statistical analyses

To confirm a hyperbolic relationship between hyperglycemic clamp-measured insulin sensitivity and first-phase insulin, we used perpendicular least squares properly weighted linear regression of log-transformed variables in R (R Foundation for Statistical Computing, Vienna, Austria), an approach that has been previously described in detail (13,28,29). For this procedure, it is necessary to provide the ratio of the variance of error perturbing the dependent variable to that of the independent variable, which was determined from coefficients of variation calculated from previously published data for euglycemic clamp-measured insulin sensitivity, hyperglycemic clamp-measured insulin sensitivity, and hyperglycemic clamp-measured first-phase insulin (14). This method was used to calculate the slope of the regression line for each of the NW, OB-NGT, OB-IGT, and OB-T2DM groups. The bootstrap method with 1,000 replications was used to calculate 95% CIs for each group. The following criteria to confirm a curvilinear-hyperbolic relationship between hyperglycemic clamp-measured insulin sensitivity and first-phase insulin were used: *1*) the slope of the regression line was near −1 and 2) the 95% CI of the slope excluded zero (28).

Differences in continuous variables were determined by univariate ANOVA with Bonferroni post hoc adjustment for multiple comparisons, and categorical variables were evaluated by χ^2 analysis using PASW 18 software (SPSS Inc., Chicago, IL). Differences across groups in DI were also adjusted for age. Spearman correlations were used to describe the relationship between variables because insulin sensitivity and DI were non-normally distributed. Bland-Altman analysis was used to evaluate concordance between 2cDI and hcDI for the total group using GraphPad Prism 5.04 software (GraphPad Inc., La Jolla, CA). Data are presented as mean ± SEM. A value of $P \leq 0.05$ was considered statistically significant and $P \leq 0.10$ was a trend.

RESULTS

Subject characteristics

There were no significant differences in sex or race distribution across the four glucose tolerance categories (Table 1). Age and Tanner stage distribution were significantly different across the four groups ($P < 0.001$), with NW having the youngest participants and more prepubertal subjects. By design, the overweight/obese groups had greater BMI, BMI percentile, and percentage of body fat than the NW group, and HbA_{1c} was greater in the OB-T2DM than in the nondiabetic groups.

Hyperbolic relationship between hyperglycemic clamp-measured insulin sensitivity and first-phase insulin

The relationship between insulin sensitivity and first-phase insulin from the hyperglycemic clamp was hyperbolic in each group. Plots for each of the groups with data fitted to a hyperbolic curve (based on the function y = constant/x) illustrate the curvilinear shape of hyperglycemic clamp-measured insulin sensitivity plotted against first-phase insulin (Fig. 1). The slope of the regression between log (IS_{Hyp}) and log(first-phase insulin) was −1.07 (95% CI −1.42 to −0.82) in NW, −0.75 (−0.91 to −0.60) in OB-NGT, −0.60 (−0.83 to −0.42) in OB-IGT, and −1.21 (−1.60 to −0.84) in OB-T2DM.

Correlation among hcDI, 2cDI, and insulin sensitivity variables

Insulin sensitivity, IS_{Hyp}, correlated with IS_{Eu} (r = 0.90, $P < 0.001$) in the total group and in each of the four groups separately ($r \geq 0.66$, $P < 0.001$ for each; Fig. 2). Similarly, hcDI correlated with 2cDI in all the groups combined (r = 0.85, $P < 0.001$) and within each group separately ($r \geq 0.62$, $P < 0.001$; Fig. 2).

Table 1—*Subject characteristics for NW, OB-NGT, OB-IGT, and OB-T2DM*

	NW (1)* $n = 73$	OB-NGT (2)* $n = 168$	OB-IGT (3)* $n = 57$	OB-T2DM (4)* $n = 32$	P ANOVA	Post hoc 1 vs. 2	1 vs. 3	1 vs. 4	2 vs. 3	2 vs. 4	3 vs. 4
Age (years)	11.5 ± 0.2	13.9 ± 0.2	14.7 ± 0.3	15.0 ± 0.3	<0.001	<0.001	<0.001	<0.001	NS	0.04	NS
Sex (%)					0.19						
Male	48	47	32	41							
Female	52	53	68	59							
Race (%)					0.57						
African American	42	46	38	50							
Caucasian	58	51	60	50							
Biracial	0	3	2	0							
Tanner stage (%)					<0.001						
I	48	5	0	0							
II-III	29	31	16	9							
IV-V	23	64	86	91							
BMI (kg/m^2)	18.0 ± 0.2	33.3 ± 0.5	36.8 ± 0.8	36.4 ± 0.9	<0.001	<0.001	<0.001	<0.001	0.001	0.04	NS
BMI percentile	50.6 ± 2.5	97.2 ± 0.2	98.8 ± 0.1	98.9 ± 0.1	<0.001	<0.001	<0.001	<0.001	NS	NS	NS
Body fat (%)	17.8 ± 0.8	41.4 ± 0.6	44.4 ± 0.7	42.5 ± 1.2	<0.001	<0.001	<0.001	<0.001	0.04	NS	NS
HbA_{1c} (%)	5.3 ± 0.06	5.3 ± 0.03	5.4 ± 0.06	6.6 ± 0.1	<0.001	NS	NS	<0.001	NS	<0.001	<0.001

Data are presented as mean ± SEM or as indicated. *Numbers in parentheses refer to group numbers in post hoc analysis.

Concordance and pattern of hcDI and 2cDI among the four groups

The hcDI and 2cDI showed a similar and significantly declining pattern across the four groups (Fig. 3*A*). Because of the lower insulin sensitivity in obesity, hcDI and 2cDI were lower in the three obese groups than in the NW youth ($P < 0.001$). Furthermore, 2cDI and hcDI were lower in OB-T2DM and in OB-IGT than in OB-NGT ($P < 0.01$) because of lower first-phase insulin (4). The hcDI was higher than 2cDI in the total group (770 ± 32 vs. 608 ± 28 mg/kg/min, $P < 0.001$ by paired *t* test), and in NW, OB-NGT, and OB-T2DM groups separately, with a trend in OB-IGT (Fig. 3*A*) due to the component of glucose-stimulated glucose disposal (30).

In the groups combined, Bland-Altman analysis revealed that hcDI values were, on average, 161.6 mg/kg/min (27%) greater than 2cDI due to the component of glucose-stimulated glucose disposal (Fig. 3*B*) (30). Specifically, within NW, OB-NGT, OB-IGT, and OB-T2DM groups separately, hcDI was 21%, 32%, 11%, and 87% greater than 2cDI, respectively.

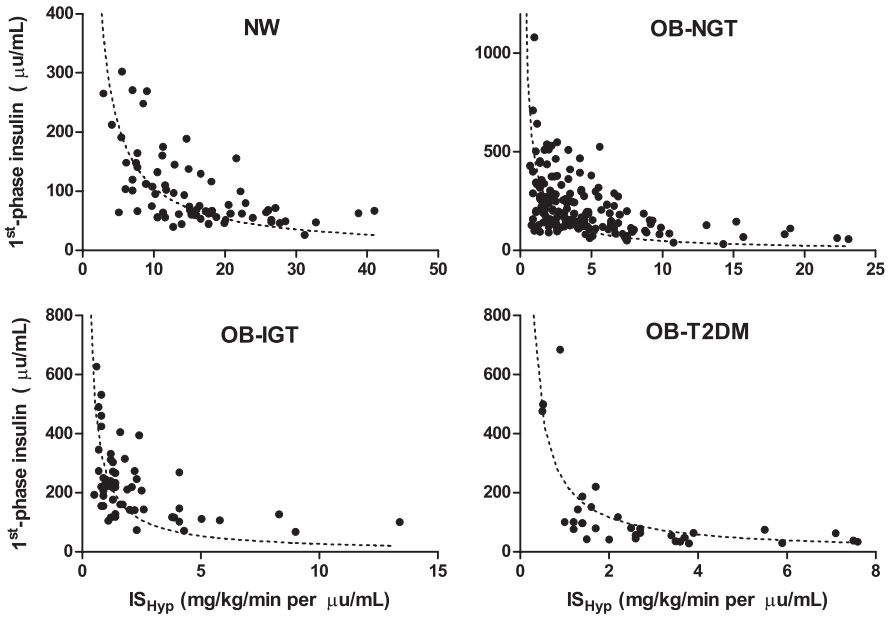

Figure 1—*Scatter plots of IS_{Hyp} vs. first-phase insulin fitted with a hyperbolic curve (based on the function* y = *constant*/x*).*

CONCLUSIONS—The current results justify the use of a single hyperglycemic clamp to provide a measure of β-cell function relative to insulin sensitivity, obviating the need for two separate clamp experiments in youth. Specifically, the data demonstrate: *1*) a hyperbolic relationship between hyperglycemic-clamp measured insulin sensitivity and first-phase insulin; *2*) a significant correlation between DI calculated from a single hyperglycemic clamp and DI calculated from the combination of two clamps, the hyperinsulinemic-euglycemic and hyperglycemic clamps; *3*) a parallel pattern of declining hcDI and 2cDI across the groups from normal glucose tolerance to impaired glucose tolerance to type 2 diabetes; and lastly *4*) a higher hcDI than 2cDI secondary to the component of glucose-stimulated glucose disposal in a hyperglycemic clamp (225 mg/dL) versus an euglycemic clamp (100 mg/dL).

Insulin sensitivity and insulin secretion play a major role in the pathophysiology of glucose dysregulation (3–5).

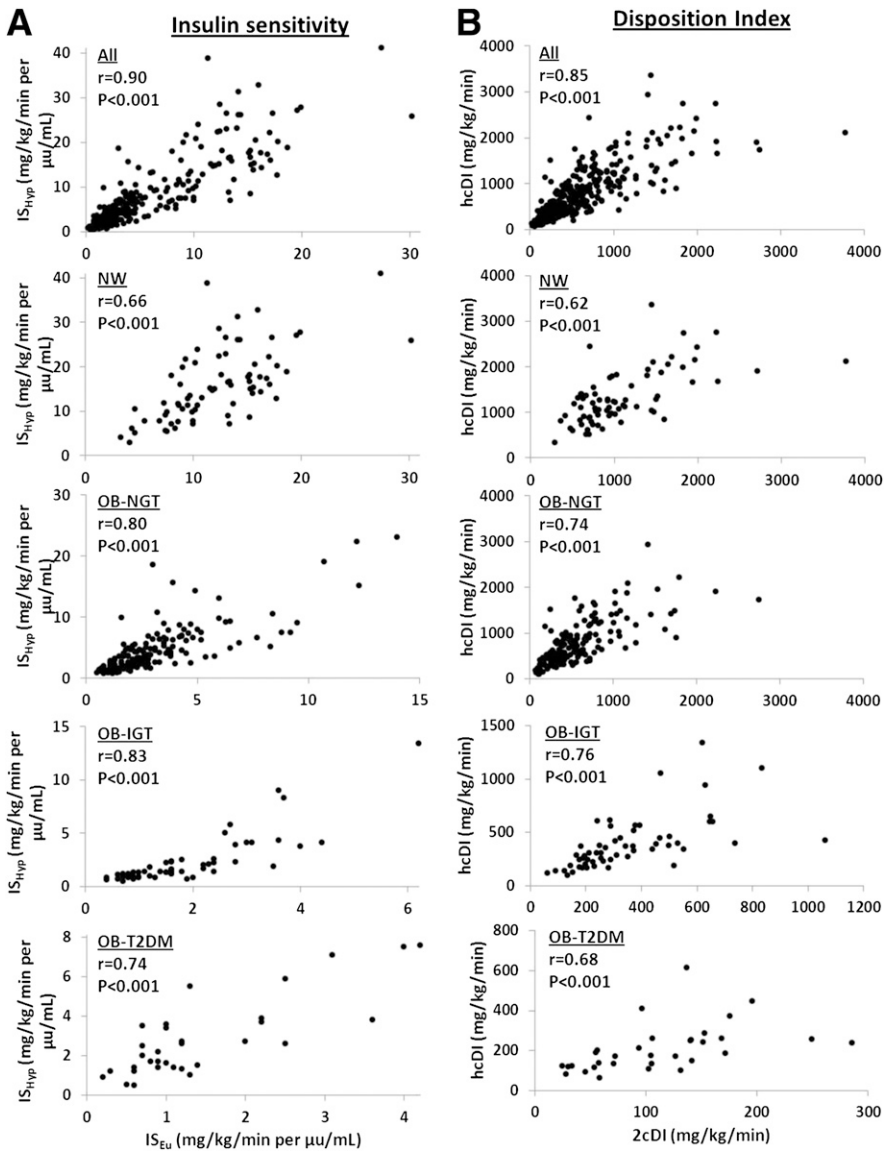

Figure 2—A: *Scatter plots of IS_{Hyp} vs. IS_{Eu}.* B: *Scatter plots of hcDI vs. 2cDI in the total group and in each of the NW, OB-NGT, OB-IGT, and OB-T2DM groups.*

Indeed, β-cell function relative to insulin sensitivity, the DI, is an established metabolic predictor of progression to diabetes (13,31). We (4,22) and others (32,33) have reported that DI decreases progressively across the spectrum of deteriorating glycemia in youth. Evaluating insulin secretion alone provides limited information regarding glucose regulation because β-cell function is tightly coupled to insulin sensitivity and both must be evaluated such that β-cell function is expressed for the prevailing insulin sensitivity (5–7). Currently established methods for evaluating DI include the FSIVGTT with minimal model analysis (34), the combined use of the hyperinsulinemic-euglycemic and hyperglycemic clamps as discussed here, and most recently, mathematical modeling of oral or intravenous tests (9,10) and estimation using an OGTT dubbed "oral DI" (11–13). Use of a hyperglycemic clamp alone is akin to the FSIVGTT, in that one test is used and test conditions are meant to simulate a hyperglycemic "stimulated" state, as a dextrose bolus (as with the FSIVGTT) or clamped at a constant plasma glucose concentration. In both methods, the insulin sensitivity and secretion components of DI are measured during the same test (although during different time phases) and, therefore, are acquired under the same overarching physiologic and environmental conditions.

Our correlations for insulin sensitivity derived from the euglycemic versus the hyperglycemic clamp ranged from $r = 0.66$ to $r = 0.90$, which are similar to studies in adults reporting correlations of $r = 0.63$ and $r = 0.84$ (14,15) but are higher than $r = 0.45$ found in the only other study in children comparing these two methods (35). These differences between the two pediatric studies could be attributable to the latter study being smaller ($n = 31$) and/or including younger (aged 6–12 years) children for whom glucose tolerance status was not reported. In parallel with the significant correlations in insulin sensitivity, but more importantly, hcDI significantly correlated with 2cDI, with correlations ranging from $r = 0.62$ to $r = 0.85$, indicating that hcDI is a useful measure of β-cell function relative to insulin sensitivity in youth. Interestingly, the weakest correlations were observed in the NW group, whereas the strongest correlations were observed in the OB-NGT and OB-IGT groups. We speculate that this could be explained by the greater variation in glucose-insulin dynamics under physiological conditions among NW subjects with a wide range of BMI (5th to <85th percentile) compared with the obese groups with a narrower range of BMI and under pathophysiological circumstances of obesity and glucose intolerance, thereby reducing the amount of variation in insulin sensitivity (and DI) within each group.

However, although hcDI was significantly correlated with 2cDI, the hcDI values were higher than the 2cDI values. This is likely attributable to the difference in conditions of the two clamps, in that one is performed under hyperglycemic conditions of ~225 mg/dL, resulting in greater glucose-stimulated glucose disposal compared with the other under euglycemic conditions of ~100 mg/dL. Indeed, glucose-stimulated glucose disposal, or "glucose effectiveness," increases with increasing hyperglycemia because glucose clearance from blood to body tissues is mediated by insulin-independent and insulin-dependent mechanisms to maintain appropriate glucose homeostasis (30,36). In agreement, previous reports in adults and one in children reported greater values of whole-body insulin sensitivity from the hyperglycemic versus euglycemic clamp (15,35,37). The data in our cohort are consistent with the latter, showing a 38% higher insulin sensitivity measured during the hyperglycemic versus the euglycemic clamp (6.5 ± 0.4 vs. 4.7 ± 0.3 mg/kg/min per μU/mL, $P < 0.001$). Furthermore, the higher

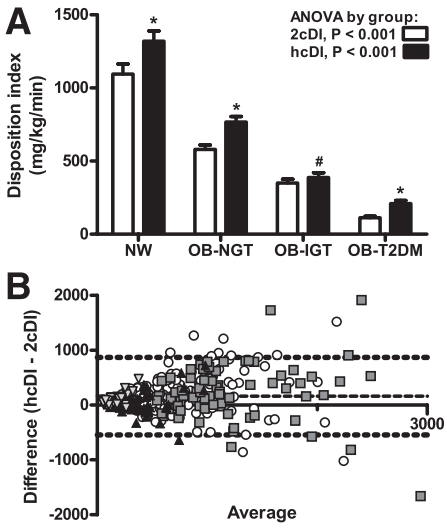

Figure 3—A: *Two-clamp disposition index for 2cDI vs. hcDI across the NW, OB-NGT, OB-IGT, and OB-T2DM groups.* *P $<$ *0.05 and* #P $<$ *0.10: one-tailed paired* t *test between 2cDI and hcDI within each group.* B: *Bland-Altman plot of hcDI vs. 2cDI in youth. Data were paired (hcDI, 2cDI) for each subject and plotted as the average vs. the difference of the paired values in the overall group* (N = *330), illustrated separately for NW (open circles), OB-NGT (gray squares), OB-IGT (black up triangles), and OB-T2DM (gray down triangles). The dashed line represents the mean bias between the two methods and the two dotted lines indicate the 95% limits of agreement.*

magnitude of the difference between the hcDI and 2cDI in type 2 diabetes (87%) versus the other groups could be a reflection of the relatively greater role that glucose-stimulated glucose disposal assumes under conditions of insulin deficiency and hyperglycemia, as reported in patients with type 2 diabetes compared with matched controls without diabetes (38). An alternative possibility is that during the hyperglycemic clamp, the reliance on endogenous insulin secretion, the denominator in the insulin sensitivity calculation, results in a bias toward a higher insulin sensitivity and DI because the endogenous insulin secretion is low/impaired in patients with diabetes. Mathematical modeling of glucose effectiveness during the hyperglycemic clamp may help elucidate the roles of glucose- versus insulin-stimulated glucose disposal under different glycemic conditions among groups of differing weight and glucose tolerance status (39).

The strengths of our investigation are that we examined a large cohort of 330 youth, including NW to obese, and those with NGT, IGT, and diabetes. In addition to correlations, which are reported for insulin sensitivity derived from the hyperglycemic versus euglycemic clamp (14,15,35), we present Bland-Altman analysis to assess agreement between these two methods.

A potential weakness of this report is that patients with diabetes were receiving metformin and/or insulin, which may have affected their DI measurement; however, any interference that might produce would be uniform for both hcDI and 2cDI calculations. Moreover, it may not be ethical to conduct clamp studies before the initiation of treatment.

Another potential weakness is that insulin sensitivity and first-phase insulin may be intrinsically related because they were both derived from the same experiment in the hyperglycemic clamp. However, insulin sensitivity during the hyperglycemic clamp was calculated during the last 60 min of the 2-h clamp, whereas first-phase insulin was calculated within the first 10 min after the bolus injection of glucose. This is akin to the minimal model analysis of a single FSIVGTT for acute insulin response to glucose (0–10 min) and insulin sensitivity (modeled at ≥10 min), which was the first proposed and is a very frequently used and popularized method for DI (5,6,40).

Another perceived weakness is that a 2-h hyperglycemic clamp may not be sufficient for a steady state to be achieved for the calculation of insulin sensitivity during the last 60 min. However, because the hyperglycemic clamp was 2 h in all participants, the bias introduced by not having reached steady state would exist across all the groups.

Finally, the slope and 95% CI of the slope for log-transformed hcDI variables was not as close to −1 in the OB-IGT group as in the other groups, which may appear to undermine the appropriateness of this method in obese children with glucose intolerance. However, this could be due to the poor reproducibility of the OGTT, whereby categorizing an individual as IGT without a second documented OGTT may not necessarily reflect the person's true glucose tolerance status, as we previously showed (24).

In conclusion, these data support the prudent use of the hyperglycemic clamp alone to measure insulin sensitivity and secretion and calculate DI, a measure of β-cell function relative to insulin sensitivity in youth. However, hcDI cannot be substituted for or directly compared with 2cDI because it is derived under hyperglycemic conditions resulting in a higher estimation of insulin sensitivity and DI. Finally, with the escalating rates of prediabetes and type 2 diabetes in youth, together with the extreme paucity of effective therapies, there is a dire need to test new therapeutic agents and their mechanism of action in modulation of the pathophysiology of type 2 diabetes. Therefore, when the combination of two clamps is not feasible due to excessive burden, or lack of participant/parent acceptability, or escalating research costs, the hcDI may be reliably used as an alternative method to evaluate β-cell function relative to insulin sensitivity in this population.

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L.S. analyzed data and first-authored the manuscript. S.L., H.T., and F.B. contributed participants to the research project, contributed data, and reviewed the manuscript. M.B. provided statistical analysis and reviewed the manuscript. S.A. provided the study concept, design, and analytical approach; acquired data; obtained funding; provided administrative, technical, and material support; supervised the study; and critically reviewed and edited the manuscript. S.A. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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