

Declining β -Cell Function Relative to Insulin Sensitivity With Escalating OGTT 2-h Glucose Concentrations in the Nondiabetic Through the Diabetic Range in Overweight Youth

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OBJECTIVE—Overweight in youth is associated with the risk of developing type 2 diabetes. We hypothesized that β -cell function relative to insulin sensitivity decreases with increasing 2-h glucose levels based on an oral glucose tolerance test (OGTT) in overweight youth.

RESEARCH DESIGN AND METHODS—A total of 147 overweight (BMI \geq 85th percentile for age and sex) youth, aged 8 to $<$ 20 years, undertook three tests: 1) a 3-h hyperinsulinemic-euglycemic clamp; 2) a 2-h hyperglycemic clamp; and 3) a 2-h OGTT. Participants were categorically assigned to five groups according to their OGTT 2-h plasma glucose level, ranging from $<$ 120 to \geq 200 mg/dL. β -Cell function relative to insulin sensitivity, assessed by clamp disposition index (DI) and oral disposition index (DI_O), were compared among groups.

RESULTS—Insulin sensitivity, first-phase insulin, and DI declined significantly as 2-h glucose concentrations increased. The highest DI was found in youth with 2-h plasma glucose concentrations $<$ 120 mg/dL, with a significant decline of \sim 40% in those with glucose concentrations between 120 and $<$ 140 mg/dL, and an \sim 75% decline, the lowest DI, in youth with glucose concentrations \geq 200 mg/dL. Data were similar with regard to the OGTT DI_O.

CONCLUSIONS—These data in overweight youth demonstrate that impairment in insulin secretion relative to insulin sensitivity is apparent even with normal glucose tolerance. Below the current cutoff of 140 mg/dL for impaired glucose tolerance, there is a $>$ 30% decline in β -cell function relative to insulin sensitivity. Against this backdrop of metabolically heightened risk for type 2 diabetes, preventive measures should target the β -cell alongside insulin sensitization.

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The transition from normal glucose tolerance (NGT) to overt type 2 diabetes is characterized by an intermediate state of prediabetes, termed impaired glucose tolerance (IGT) (1). Insulin resistance and the inability of the β -cells to adequately compensate through increased insulin secretion characterize the progression to IGT in adults (2,3). Whether alterations in glucose tolerance in youth are

similarly characterized is uncertain. Cross-sectional data from our group demonstrated that insulin sensitivity is \sim 50% lower in obese adolescents with type 2 diabetes than in equally obese control subjects, and first-phase insulin secretion is \sim 75% lower (4). Obese adolescents with IGT, however, had similar glucose disposal as youth with NGT but significantly lower first-phase insulin secretion and

reduced disposition index (DI), a measure of β -cell function relative to insulin sensitivity (5). Longitudinal data in obese adolescents progressing to IGT suggest that individuals with IGT manifest primary defects in β -cell function, which is aggravated by declining insulin sensitivity (6,7).

Despite this, observations in overweight/obese youth are sparse with respect to β -cell function and insulin sensitivity across the spectrum of 2-h glycemia from NGT to type 2 diabetes. Moreover, the level of glycemia at which β -cell dysfunction presents is uncertain. In one study of 4- to 20-year-old obese individuals with NGT, oral glucose tolerance test (OGTT)-derived whole-body insulin sensitivity index declined in subjects with 2-h glucose concentrations \geq 100 mg/dL, and the insulinogenic index was impaired in those with glucose concentrations between 120 and 139 mg/dL compared with those with 2-h glucose concentrations $<$ 100 mg/dL (8). Our group recently demonstrated impaired β -cell function relative to insulin sensitivity within the nondiabetic fasting glucose range in children (9). At the presently accepted cutoff of 100 mg/dL for impaired fasting glucose, there was an \sim 49% decline in the DI independent of obesity (9). Therefore, the current study of overweight youth investigated the relationship between 2-h OGTT glucose levels and insulin secretion relative to insulin sensitivity using clamp techniques. In addition, oral DI (DI_O), shown to predict the development of diabetes in adults (10), was assessed from the OGTT. We hypothesized that β -cell function relative to insulin sensitivity declines as OGTT 2-h glucose concentrations increase from the normal to the diabetic range.

RESEARCH DESIGN AND METHODS

Participants were 147 black, white, and biracial overweight (BMI \geq 85th percentile for age and sex) youth, aged 8 to $<$ 20 years, recruited through

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Two-hour glucose levels and disposition index

advertisement. Some participants were reported previously as part of an ongoing grant (11,12). Procedures took place after institutional review board approval, parental written informed consent, and participant assent. Participants were screened by medical history, physical examination, and hematological and biochemical tests (Table 1). All were Tanner stages II–V. Sixty-one female subjects had untreated polycystic ovary syndrome (PCOS). None were taking medications known to affect glucose tolerance. Twenty-one participants had type 2 diabetes with negative pancreatic auto antibodies (13). At the time of the evaluation, 7 patients were on lifestyle modification and 14 were on metformin. Metformin was discontinued 48 h before clamp studies (13). Youth on metformin or lifestyle modification were included to assess if despite insulin sensitization β -cell function contributes to 2-h glucose determination. No other participants were taking medications known to affect glucose tolerance.

Body composition and abdominal adipose tissue

Body composition was assessed using dual-energy X-ray absorptiometry (11). Abdominal subcutaneous and visceral adipose tissues were determined at L4–L5 by a computed tomography scan in 111 subjects (11) and a magnetic resonance

scan in 36 subjects (14). The change in methodology was dictated by the study section during grant renewal.

Participants maintained free-living conditions during the experimental period. None were participating in organized sports. We prescribed a weight-maintaining diet containing 55% carbohydrate, 30% fat, and 15% protein during the investigation. Each participant undertook three tests on separate occasions after a 10- to 12-h overnight fast: 1) a 3-h hyperinsulinemic-euglycemic clamp; 2) a 2-h hyperglycemic clamp; and 3) a 2-h OGTT.

Hyperinsulinemic-euglycemic clamp

In vivo insulin sensitivity was assessed using a 3-h hyperinsulinemic-euglycemic clamp. During the clamp, intravenous crystalline insulin (Humulin; Lilly, Indianapolis, IN) was infused at a constant rate of 80 mU/m²/min (5). Plasma glucose was clamped at 100 mg/dL with a variable-rate infusion of 20% dextrose based on arterialized plasma glucose determined every 5 min.

Hyperglycemic clamp

A 2-h hyperglycemic clamp was performed to evaluate first- and second-phase insulin secretion (5,11). In brief, glucose was acutely elevated to 225 mg/dL and clamped at that level with a variable-rate infusion of 20% dextrose in water. Blood samples for

insulin were obtained every 2.5 min for the first 15 min and then every 15 min until the end.

OGTT

Participants underwent an OGTT (1.75 g/kg, maximum 75 g) (5). Blood samples were obtained at –15, 0, 15, 30, 60, 90, and 120 min for the measurement of glucose and insulin.

Biochemical measurements

Plasma glucose was measured by the glucose oxidase method using a glucose analyzer (Yellow Springs Instruments, Yellow Springs, OH). Plasma insulin was determined by radioimmunoassay (11,13), and HbA_{1c} was measured by high-performance liquid chromatography (Tosoh Medics) (13).

Calculations

The insulin-stimulated glucose disposal rate was calculated during the last 30 min of the euglycemic clamp to be equal to the rate of exogenous glucose infusion. Peripheral insulin sensitivity was calculated by dividing the insulin-stimulated glucose disposal rate by steady-state plasma insulin concentrations during the last 30 min of the clamp, multiplied by 100 (11,12). During the hyperglycemic clamp, first-phase insulin was calculated as the mean of five determinations every 2.5 min during the

Table 1—Characteristics of the participants by categories of 2-h plasma glucose concentration (mg/dL) during the OGTT

Variable	Categories by OGTT 2-h plasma glucose concentration					P ANOVA
	<120	120 to <140	140 to <160	160 to <200	≥200	
n	45	31	33	23	15	
Sex (male/female)	17/28	12/19	13/20	6/17	6/9	NS
Ethnicity (black/white/biracial)	21/22/2	12/17/2	12/21/0	6/16/1	9/6/0	NS
PCOS	20/28	13/19	15/20	7/17	4/9	NS
Age (years)	14.9 ± 0.3	14.7 ± 0.3	14.4 ± 0.4	15.2 ± 0.4	15.2 ± 0.7	NS
Tanner stages II and III	7	5	6	2	3	NS
Tanner stages IV and V	38	26	27	21	12	NS
Height (cm)	165.6 ± 1.6	164.9 ± 1.2	164.3 ± 1.4	164.0 ± 2.0	164.1 ± 3.0	NS
Weight (kg)	98.2 ± 3.6	95.6 ± 2.5	98.9 ± 3.7	98.8 ± 4.1	102.3 ± 6.7	NS
BMI (kg/m ²)	35.4 ± 1.1	35.1 ± 0.9	36.5 ± 1.1	36.6 ± 1.3	37.5 ± 1.6	NS
BMI percentile	97.8 ± 0.4	97.9 ± 0.3	98.8 ± 0.2	98.7 ± 0.2	99.2 ± 0.2	0.021
Fat mass (kg)	41.0 ± 2.2	41.3 ± 1.6	41.8 ± 2.0	43.5 ± 2.3	38.0 ± 3.1	NS
Percentage body fat	43.1 ± 1.1	44.0 ± 0.9	43.7 ± 0.9	44.9 ± 1.0	42.6 ± 1.4	NS
Waist circumference (cm)	107.7 ± 3.0	101.6 ± 2.6	107.4 ± 2.6	105.7 ± 3.2	113.2 ± 4.7	NS
Visceral fat (cm ²)	66.2 ± 5.3 ^a	82.0 ± 8.2	74.3 ± 4.9	87.0 ± 6.5	100.2 ± 14.3 ^a	0.031
Subcutaneous abdominal fat (cm ²)	526.8 ± 34.6	480.6 ± 25.9	542.7 ± 29.1	566.0 ± 30.9	529.4 ± 41.8	NS
Total abdominal fat (cm ²)	586.9 ± 36.4	572.9 ± 30.3	617.0 ± 32.2	653.0 ± 35.6	629.6 ± 48.0	NS
Percentage visceral fat	11.8 ± 0.8	15.6 ± 1.7	12.2 ± 0.6	13.3 ± 0.7	16.3 ± 1.8	0.022
Percentage subcutaneous fat	88.2 ± 0.8	84.4 ± 1.7	87.8 ± 0.6	86.7 ± 0.7	83.7 ± 1.8	0.022

Data are means ± SE. Groups with the same letter differ significantly ($P < 0.05$). NS, not significant.

first 10 min after the bolus dextrose injection. DI was calculated as the product of insulin sensitivity times first-phase insulin (5,11).

Using OGTT data, insulin sensitivity was estimated by $1/\text{fasting insulin}$ (15) and early insulin response, the insulinogenic index, as $\Delta \text{insulin (0–30 min)} (\mu\text{U/mL})/\Delta \text{glucose (0–30 min)} (\text{mg/dL})$ (16,17). DI_O was calculated as the product of $1/\text{fasting insulin} \times \text{insulinogenic index}$ ($\Delta I_{0-30}/\Delta G_{0-30}$) (10). Recently, a nonlinear function describing the relationship between the oral glucose-induced early insulin response and insulin sensitivity has been used to assess β -cell function in both observational (18) and interventional studies in adults (19). Moreover, we chose these OGTT-derived indices of insulin sensitivity and secretion because they correlate well with clamp measures in children (17,20), are easily calculated in epidemiological or intervention studies, and recently have been used to calculate DI_O predicting diabetes development in adults (10).

Statistical analysis

Statistics were performed using SPSS version 18.0. Participants were grouped into five categories according to OGTT 2-h plasma glucose concentration: <120 , 120 to <140 (NGT groups), 140 to <160 , 160 to <200 (IGT groups), and ≥ 200 mg/dL (diabetic group). A similar approach was used in adults (21). This categorization of accepted ranges for diagnosis of glucose tolerance was chosen to help characterize the glycemic level at which β -cell dysfunction presents. One-way ANOVA compared group differences in participants, insulin sensitivity, first-phase insulin, DI, $1/\text{fasting insulin}$, insulinogenic index, and DI_O . Two-way ANOVA independently examined the effects of sex and race upon these data. Bonferroni post hoc *t* tests were used to identify group differences. Categorical variables (sex, race, Tanner stage, and PCOS) were compared using χ^2 tests. Stepwise multiple regression assessed the contribution of age, race, Tanner stage, sex, BMI, and DI to 2-h glucose. Data are presented as means \pm SE. Significance was set at $P < 0.05$.

RESULTS

Participant characteristics

Participant characteristics are summarized in Table 1. There were no differences in sex,

race, age, pubertal development, or the number of girls with PCOS among the groups. Groups had similar body weight, BMI, body composition, and waist circumference. Visceral fat was higher in the group with 2-h glucose concentrations ≥ 200 mg/dL compared with concentrations <120 mg/dL.

Glycemic profile

Figure 1 shows fasting and 2-h glucose and insulin concentrations and HbA_{1c} by group. Fasting glucose was significantly higher in the group with 2-h glucose concentrations ≥ 200 mg/dL compared with all other groups (Fig. 1A). Fasting insulin concentrations differed significantly between groups with the lowest and the highest 2-h glucose (Fig. 1B). The 2-h plasma glucose concentrations differed among groups by design (Fig. 1C). The 2-h insulin concentrations were significantly higher in groups with 2-h glucose concentrations between 120 and <200 mg/dL than in those with concentrations <120 mg/dL (Fig. 1D). As expected, HbA_{1c} was significantly higher in the group with a 2-h glucose concentration ≥ 200 mg/dL compared with all other groups (Fig. 1E).

In vivo insulin sensitivity and secretion

Figure 2 shows insulin sensitivity from the euglycemic clamp, first-phase insulin from the hyperglycemic clamp, and DI by OGTT 2-h glucose categories. ANOVA across groups showed a significant trend for declining insulin sensitivity (Fig. 2A) and first-phase insulin (Fig. 2B) as 2-h glucose increased, and both differed significantly at the extremes of the glucose categories (<120 mg/dL vs. ≥ 200 mg/dL). After adjusting for age, sex, race/ethnicity, Tanner stage, BMI percentile, and visceral fat using ANCOVA, first-phase insulin remained significantly different ($P = 0.002$) but not insulin sensitivity ($P = 0.439$). Adjustment solely for visceral fat ($P = 0.225$) or BMI percentile ($P = 0.078$) also removed group differences in insulin sensitivity.

Clamp DI

DI decreased with increasing 2-h glucose levels and was significantly higher in the group with 2-h plasma glucose concentrations <120 mg/dL compared with all other groups (Fig. 2C). Results were similar after adjusting for age, sex,

race/ethnicity, Tanner stage, BMI percentile, or BMI and visceral fat.

The above analyses were performed after excluding the 61 subjects with PCOS. Results were similar for first-phase insulin and DI, but differences in insulin sensitivity among groups lost significance.

OGTT-derived indices and DI_O

Figure 3 shows OGTT-derived insulin sensitivity ($1/\text{fasting insulin}$), insulinogenic index, and DI_O by 2-h glucose level. Insulin sensitivity did not differ among groups (Fig. 3A). There was a significant trend for the insulinogenic index to decline with increasing 2-h glucose concentrations, and it was highest in the group with 2-h glucose concentrations <120 mg/dL and differed significantly from the group with 2-h glucose concentrations ≥ 200 mg/dL (Fig. 3B). DI_O in the group with 2-h plasma glucose concentrations <120 mg/dL was significantly higher compared with all other categories and declined incrementally (Fig. 3C). After adjusting for age, sex, race/ethnicity, Tanner stage, BMI percentile, and visceral fat, results were unchanged.

Homeostasis model assessment of insulin sensitivity (HOMA-IS) and quantitative insulin sensitivity check index (QUICKI), additional fasting surrogate estimates of insulin sensitivity (20), were calculated to assess if they show the same trend for insulin sensitivity across glucose categories as the clamp. One-way ANOVA demonstrated both variables differed significantly across glucose categories (HOMA-IS: $P = 0.023$; QUICKI: $P < 0.001$). After adjusting for age, sex, race/ethnicity, Tanner stage, BMI percentile, and visceral fat, differences across glucose categories disappeared (HOMA-IS: $P = 0.172$; QUICKI: $P = 0.057$).

Sex and race

No sex differences were seen for fasting insulin, first-phase insulin, insulinogenic index, clamp DI, or DI_O , but clamp insulin sensitivity was significantly lower in female than in male subjects ($P < 0.001$), as previously described (22). After excluding female subjects with PCOS, sex differences in insulin sensitivity remained ($P = 0.002$). First-phase insulin was higher in black than in white subjects ($P = 0.021$), as previously described (11), but no race differences were seen in insulin sensitivity, DI, fasting insulin, insulinogenic index, or DI_O . We did not include biracial

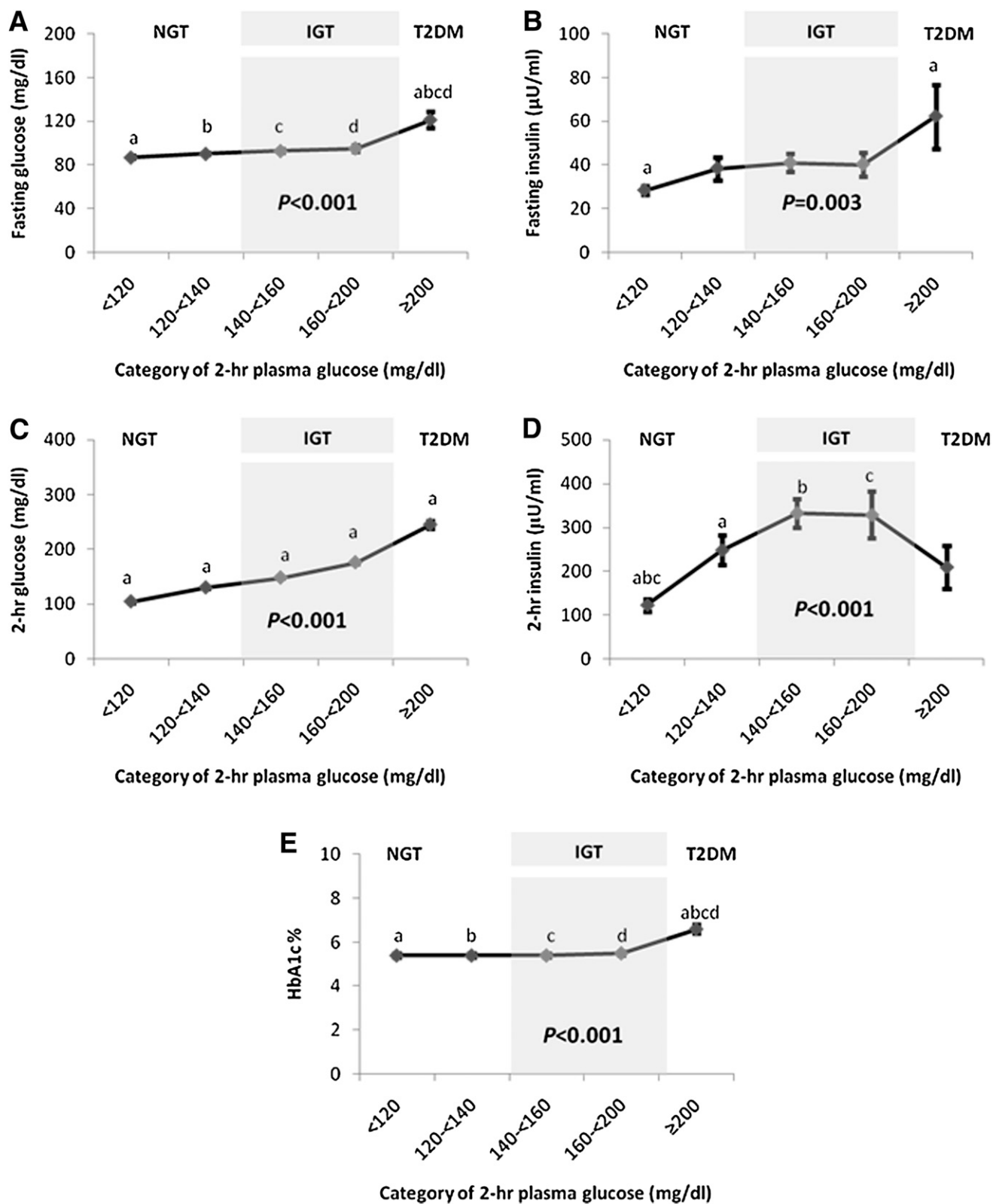


Figure 1—Fasting glucose (A) and insulin (B), OGTT 2-h glucose (C) and insulin (D), and HbA_{1c} (E) across the groups categorized according to 2-h plasma glucose levels during the OGTT. P for ANOVA. Groups with the same letter differ significantly ($P < 0.05$). T2DM, type 2 diabetes.

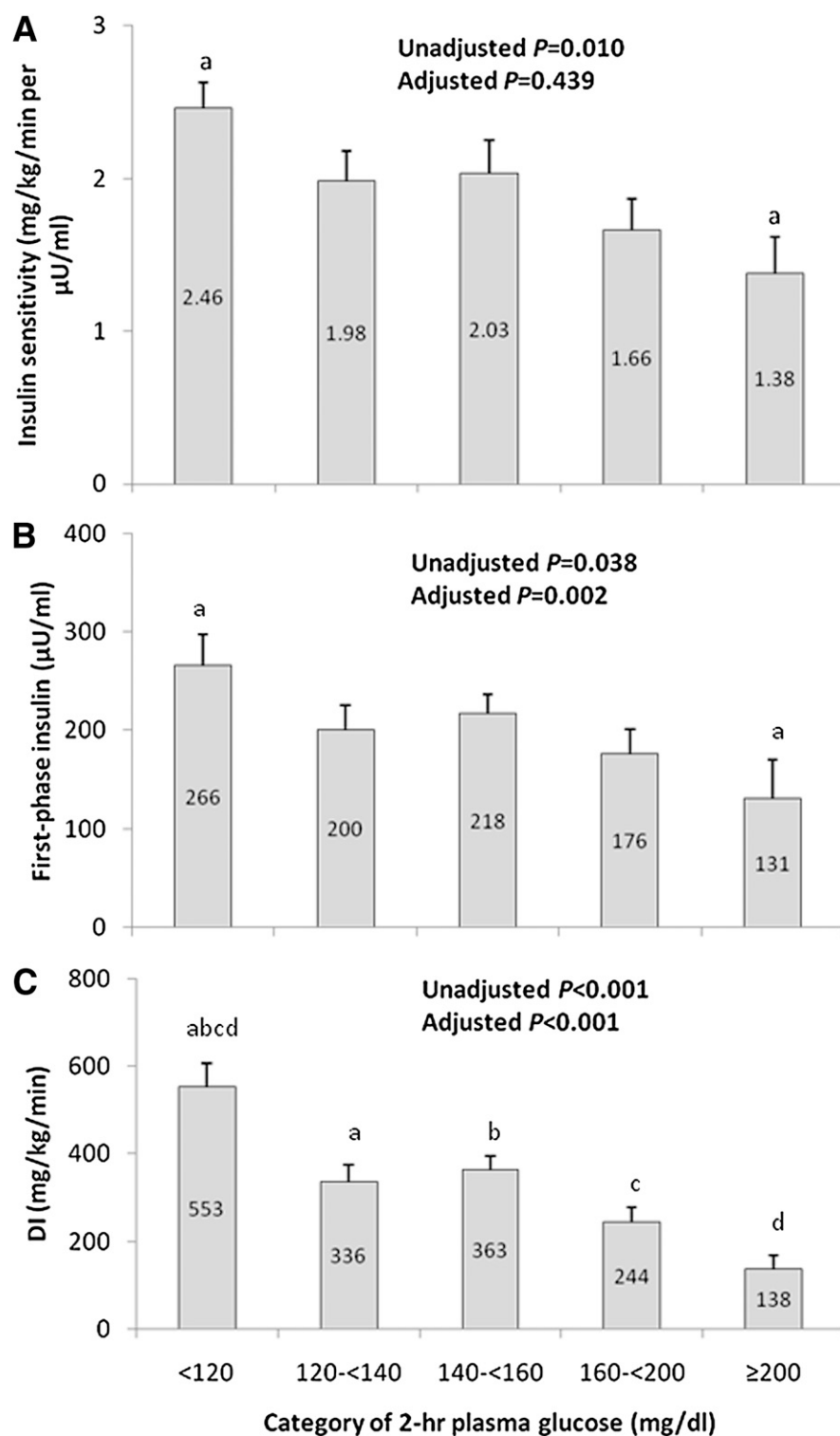


Figure 2—Insulin sensitivity from the hyperinsulinemic-euglycemic clamp (A), first-phase insulin concentration from the hyperglycemic clamp (B), and DI (C) in overweight/obese youth categorized by OGTT 2-h plasma glucose levels. Unadjusted P for ANOVA. ANCOVA adjusted P for age, sex, race/ethnicity, Tanner stage, BMI percentile, and visceral fat. Groups with the same letter differ significantly ($P < 0.05$).

participants in this analysis because they numbered only five. Data were similar after excluding female subjects with PCOS.

Correlations

OGTT 2-h glucose correlated with first-phase insulin ($r = -0.257$, $P = 0.002$), insulin sensitivity ($r = -0.258$, $P = 0.002$),

DI ($r = -0.436$, $P < 0.001$), and visceral fat ($r = 0.263$, $P = 0.002$) but not age ($r = 0.033$, $P = 0.693$), BMI ($r = 0.105$, $P = 0.206$), or percentage body fat ($r = -0.070$, $P = 0.414$). In multiple regression analysis, with 2-h glucose as the dependent variable and age, sex, race, Tanner stage, BMI, and clamp DI as the independent variables, DI independently explained 19% of the variance in 2-h glucose (DI: partial $r = -0.436$, $P < 0.001$). When BMI was replaced with percentage body fat, fat mass, or visceral fat in the analysis, none significantly predicted 2-h glucose. When participants with PCOS were removed, DI independently explained 23% of the variance ($r = -0.484$, $P < 0.001$) in 2-h glucose. Similar analysis performed with DI_0 instead of clamp DI revealed that DI_0 independently explained 21% of the variance in 2-h glucose (DI_0 : partial $r = -0.460$, $P < 0.001$).

CONCLUSIONS—The current study assessed β -cell function relative to insulin sensitivity across OGTT 2-h glucose concentrations in overweight youth. Our findings demonstrate a significant decline ($\sim 40\%$) in DI in youth with 2-h glucose concentrations in the normal range of 120 to <140 mg/dL compared with those with concentrations <120 mg/dL, escalating to $\sim 75\%$ in individuals with 2-h glucose in the diabetes range of ≥ 200 mg/dL. Thus, the present findings indicate that even youth classified as having NGT (2-h glucose concentrations 120 to <140 mg/dL) show decreased β -cell function relative to insulin sensitivity.

Our data mirror adult studies. In 6,414 Finnish male subjects from the Metabolic Syndrome in Men Study, OGTT-derived DI decreased by 41% within the normal 2-h plasma glucose range, by 60% with IGT, and by 70% in the diabetes range (23). The San Antonio Metabolism Study found that plasma insulin response in relation to the severity of insulin resistance was impaired at a 2-h plasma glucose concentrations ≥ 5.6 mmol/L (≥ 100 mg/dL), resulting from reduced insulin secretion (21). Others (24) have demonstrated similar findings. Thus, in adults decline in β -cell function relative to insulin sensitivity with increasing glycemia starts in the normal glucose range. The only pediatric study in obese youth aged 4–20 years with NGT found that those whose 2-h glucose concentrations were <100 mg/dL had greater OGTT-derived DI compared with those whose 2-h glucose concentrations were ≥ 100 mg/dL (8). The current study

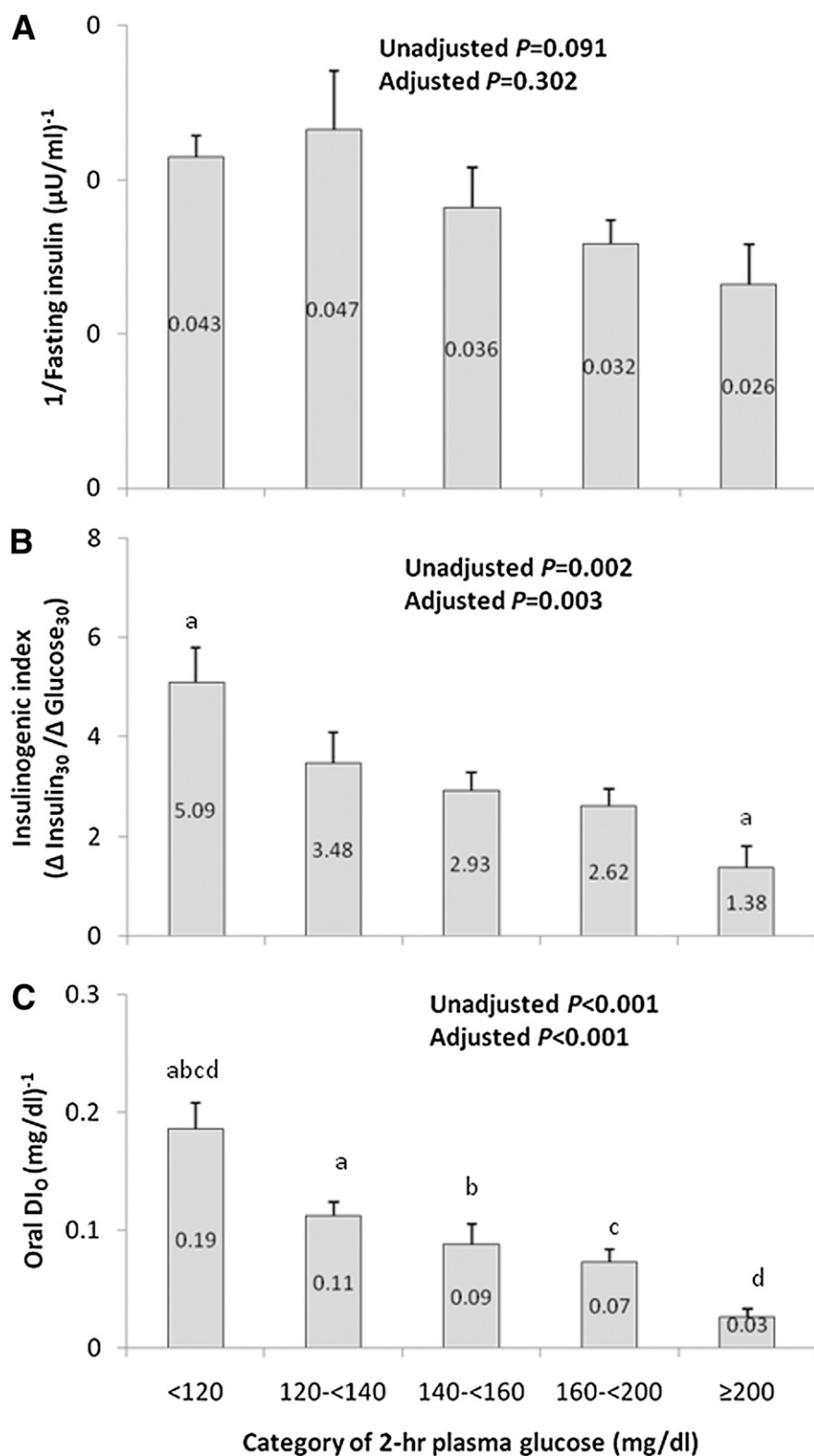


Figure 3—Insulin sensitivity ($1/\text{fasting insulin}$) (A), insulinogenic index [$\Delta \text{insulin}_{(0-30 \text{ min})} / \Delta \text{glucose}_{(0-30 \text{ min})}$] (B), and DI_O (C) calculated from the OGTT in 147 overweight and obese youth categorized by OGTT 2-h plasma glucose levels. Unadjusted P for ANOVA. ANCOVA adjusted P for age, sex, race/ethnicity, Tanner stage, BMI percentile, and visceral fat. Groups with the same letter differ significantly ($P < 0.05$).

included youth with prediabetes and diabetes and used sensitive and robust clamp methods to demonstrate DI declines further across the IGT and diabetes range. Some participants with type 2 diabetes and 2-h OGTT glucose concentrations ≥ 200 mg/dL were on metformin, but despite insulin-sensitizing therapy, in vivo insulin sensitivity was significantly lower than that in the group with glucose concentrations < 120 mg/dL, which is consistent with our previous observation (4). Our data suggest that significant decrements in DI are present in overweight youth well before any established diagnostic criteria (1) of glucose intolerance can be made, and current criteria may represent a relatively advanced stage of impairment in β -cell function relative to insulin sensitivity. This is supported by our recent investigation examining the relationship between normal fasting glucose and insulin secretion, which demonstrated that youth within the non-diabetic glucose range (> 90 to < 100 mg/dL) had evidence of impaired β -cell function relative to insulin sensitivity compared with children whose fasting glucose concentrations were ≤ 90 mg/dL (9).

The OGTT-derived DI_O showed similar findings to the clamp DI, demonstrating that impairments in insulin secretion relative to insulin sensitivity could be detected in high-risk youth at an early stage using OGTT. The OGTT, though less precise than the clamp measurements, is simpler to perform in epidemiological or intervention studies. Moreover, because DI_O predicts the development of future diabetes above and beyond fasting and 2-h glucose in adults (10), it could be used to track risk progression and/or reversal with intervention/prevention trials in obese youth at risk for type 2 diabetes. Although DI_O and the insulinogenic index demonstrated similar trends to the clamp measurements, the surrogate measure of insulin sensitivity we used ($1/\text{fasting insulin}$) showed no difference among groups. Other measures of insulin sensitivity (HOMA-IS and QUICKI) showed similar trends to the clamp data. Possibly, $1/\text{fasting insulin}$ may not account for lowered insulin secretion in the face of hyperglycemia that occurs in diabetic or glucose-intolerant subjects (15). Additional investigations need to assess surrogate estimates of insulin sensitivity against clamp measures across the spectrum of glucose tolerance in youth.

A trend of declining insulin sensitivity and first-phase insulin secretion

with escalating 2-h glucose levels contributed to the significant drop in DI across glucose categories. Within the glucose range of 120 to <140 mg/dL, there were nonsignificant declines of 25% in first-phase insulin and 20% in insulin sensitivity compared with the reference group of <120 mg/dL. These figures increased to ~51 and ~44% for insulin secretion and sensitivity, respectively, and were significant when 2-h glucose concentrations were ≥ 200 mg/dL. These data support the notion that assessing β -cell function should take into account differences in insulin sensitivity because failure to account for the coupling of insulin sensitivity and secretion could greatly underestimate the severity of any β -cell dysfunction. In addition, however, assessing insulin sensitivity should take into account the strong influence of adiposity. In the current study, after adjusting for visceral adiposity and BMI percentile, group differences in insulin sensitivity, but not first-phase insulin or DI, disappeared, suggesting that adiposity is an important determinant of insulin sensitivity. This is consistent with our previous findings that when adolescents with NGT and IGT are matched for total and visceral adiposity, the metabolic difference explaining IGT is lower insulin secretion with no difference in sensitivity (25).

In summary, our findings demonstrate that impairment in β -cell function relative to insulin sensitivity, assessed by clamp DI or DI_O , is evident even in youth who are considered to have NGT (2-h glucose concentrations 120 to <140 mg/dL) under current criteria (1). This impairment worsens as 2-h glucose levels increase. Against this backdrop of metabolically heightened risk for type 2 diabetes, measures to prevent progression from NGT to IGT to type 2 diabetes in obese youth should target β -cell function alongside insulin sensitization.

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S.F.B. analyzed data and wrote the manuscript. F.B. contributed participants to the

research project, took part in the experiments, and contributed data. S.J.L. contributed participants to the research project, took part in the experiments, contributed data, and contributed laboratory and analytical tools. H.T. and N.G. contributed participants to the research project, took part in the experiments, and contributed data. S.A.A. provided the study concept and design; acquired data; obtained funding; provided administrative, technical, and material support; supervised the study; and critically reviewed and edited the manuscript.

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