# Metabolic Contrasts Between Youth and Adults With Impaired Glucose Tolerance or Recently Diagnosed Type 2 Diabetes: II. Observations Using the Oral Glucose Tolerance Test

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## OBJECTIVE

To compare oral glucose tolerance test (OGTT) glucose, C-peptide, and insulin responses and insulin sensitivity in youth and adults with impaired glucose tolerance (IGT) or recently diagnosed type 2 diabetes.

## RESEARCH DESIGN AND METHODS

A total of 66 youth (80.3% with IGT) and 355 adults (70.7% with IGT) underwent a 3-h OGTT to assess *1*) insulin sensitivity (1/fasting insulin), *2*) C-peptide index (CPI) and insulinogenic index (IGI) over the first 30 min, and *3*) glucose, C-peptide, and insulin incremental areas above fasting over the 3-h post-ingestion (incremental glucose [G-iAUC], incremental C-peptide [CP-iAUC], and incremental insulin area under the curve [I-iAUC] responses, respectively).

## RESULTS

Fasting, 2-h glucose, and G-iAUC were similar in both age-groups, but youth had ~50% lower 1/fasting insulin ($P < 0.001$), 75% higher CPI (mean [95% CI] 0.703 [0.226, 2.183] vs. 0.401 [0.136, 1.183] nmol/mmol; $P < 0.001$), and more than twofold higher IGI (257.3 [54.5, 1,215.8] vs. 114.8 [28.0, 470.8] pmol/mmol; $P < 0.001$). Two-hour C-peptide and insulin concentrations, CP-iAUC, and I-iAUC were all higher in youth (all $P < 0.001$). C-peptide and insulin responses remained significantly greater in youth after adjustment for insulin sensitivity. Within each age-group, individuals with type 2 diabetes versus IGT had significantly lower CPI and IGI with no difference in insulin sensitivity.

## CONCLUSIONS

The balance between insulin sensitivity and β-cell responses differs between youth and adults with IGT or recently diagnosed type 2 diabetes. Despite similar postload glucose levels, youth demonstrate greater C-peptide and insulin responses that exceed what is needed to compensate for their lower insulin sensitivity. Longitudinal studies are required to determine whether this feature contributes to a more rapid decline in β-cell function in youth with dysglycemia.

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PATHOPHYSIOLOGY/COMPLICATIONS

With the epidemic of pediatric obesity (1), the number of youth with prediabetes and type 2 diabetes continues to increase rapidly (2). Cross-sectional, observational, and therapeutic trials suggest that type 2 diabetes in these younger individuals might represent a more severe and rapidly progressive condition than in adults (3). These observations provide urgency to better understand the similarities and differences in disease pathogenesis between youth and adults in order to design appropriate intervention strategies to slow or halt diabetes progression.

The Restoring Insulin Secretion (RISE) Study is examining interventional approaches to preserve or improve β-cell function in youth and adults with impaired glucose tolerance (IGT) or recently diagnosed type 2 diabetes (4). These different approaches—medical (metformin, insulin glargine, and liraglutide) and lap band surgery—are being tested in a seven-center study of youth and adults in the U.S. using common outcome measurements and a central laboratory. In this manuscript, we describe results from the oral glucose tolerance test (OGTT) performed at baseline. We compare indices of insulin sensitivity and β-cell function derived from the integrated physiologic responses to glucose ingestion in both youth and adults. These analyses parallel, complement, and expand on those made using hyperglycemic clamps that are presented in an accompanying article (5).

## RESEARCH DESIGN AND METHODS
### Participants
Youth aged 10–19 years with pubertal development assessed by a RISE Study pediatric endocrinologist to be Tanner stage ≥II (females, Tanner stage ≥II breast development; and males, testicular volume >3 mL) and adults at high risk for IGT and type 2 diabetes were screened with a 75-g OGTT and hemoglobin $A_{1c}$ ($HbA_{1c}$). To qualify, participants needed to have an elevated 2-h glucose concentration (≥7.8 mmol/L) and meet additional specific protocol-based criteria for fasting glucose and $HbA_{1c}$ as detailed in a companion article (5). Youth were required to have a BMI ≥85th percentile for age and for adults, ≥25 kg/m² (6). Additional details on participant recruitment and eligibility criteria have

been described (4), and information is available for all three protocols at the RISE website (https://rise.bsc.gwu.edu/web/rise/collaborators).

For this analysis, we combined all participants in the Adult Surgery Study (BetaFat; n = 88) and Adult Medication Study (n = 267) and compared them to 66 drug-naïve (53 with IGT and 13 with type 2 diabetes) participants in the Pediatric Medication Study. Twenty-five youth treated with metformin at baseline or previously were excluded from the present analysis to obviate potential confounding from this exposure. All adults (n = 355; 251 with IGT and 104 with type 2 diabetes) were, per protocol, naïve for glucose-lowering medications. Classification of glucose tolerance in youth and adults was based on American Diabetes Association OGTT criteria for fasting and 2-h glucose (7).

All participants gave written informed consent/assent, consistent with the Declaration of Helsinki and the guidelines of each center's institutional review board.

### Anthropometric Measurements
Anthropometric measurements were performed with participants wearing light clothing without shoes. Waist circumference was measured in a horizontal plane at the midpoint between the top of the iliac crest and the bottom of the costal margin in the midaxillary line using a fiberglass (nonstretching) tape. Height was measured in a fully vertical position using a calibrated stadiometer with the heels together. Weight was measured using a calibrated electronic scale, zeroed before each measurement. From these measurements, BMI and triponderal index (8) were calculated.

### Procedures
Following a 10-h overnight fast, a 3-h, 75-g OGTT was performed. An indwelling intravenous catheter was placed for venous sampling. After 15 min of rest, venous blood samples were drawn 10 and 5 min prior to ingesting the glucose solution, which was consumed within 5 min. Additional blood samples were obtained 10, 20, 30, 60, 90, 120, 150, and 180 min after commencing glucose ingestion. Blood samples were immediately placed on ice prior to being separated and frozen at −80°C for shipment to the central biochemistry laboratory at the University of Washington for subsequent measurement of plasma glucose, C-peptide, and insulin.

### Assays
Glucose was measured by the glucose hexokinase method using Roche reagent on a c501 autoanalyzer (Roche). C-peptide and insulin were measured by a two site immunoenzymometric assay performed on the Tosoh 2000 autoanalyzer (Tosoh Bioscience, Inc., South San Francisco, CA). The interassay coefficients of variation on quality control samples with low, medium, medium-high, and high concentrations were ≤2.0% for glucose, ≤4.3% for C-peptide, and ≤3.5% for insulin. All measures are presented in Système International units. These can be converted to conventional units using standard conversion factors with the exception of insulin, for which 0.134 should be used.

### Calculations for OGTT-Derived Measurements
#### Insulin Sensitivity and Clearance
The 1/fasting insulin (1/FI) was calculated and used as a surrogate estimate of insulin sensitivity (9,10). The ratio of fasting C-peptide to fasting insulin was used as an estimate of insulin clearance (11).

#### C-Peptide and Insulin Responses
The C-peptide index (CPI; $\Delta C_{30}/\Delta G_{30}$) and insulinogenic index (IGI; $\Delta I_{30}/\Delta G_{30}$) were calculated using the 0- and 30-min samples (12,13). The incremental glucose (G-iAUC), C-peptide (CP-iAUC), and insulin area under the curve (I-iAUC) responses above the fasting concentration over the entire 3-h sampling period were calculated as the AUC using the trapezoidal method. The ratio of the iAUC for each β-cell peptide to that for glucose (CP-iAUC/G-iAUC and I-iAUC/G-iAUC) was calculated as an additional measure of the β-cell response accounting for the prevailing glucose stimulus.

#### Glucose Tolerance
Individuals were classified as having IGT or diabetes based on the 2-h glucose concentration (7). The 3-h G-iAUC above fasting was also used as a measure of glucose tolerance.

### Data Management and Statistical Analysis
All analyses were performed using SAS (SAS Institute, Cary, NC) and R (The R Foundation). Descriptive statistics include percentages, mean ± SD, or geometric means and 95% CI for nonnormally distributed data. For the latter, P values were calculated from log-transformed data. Comparisons between any two groups

were computed using $\chi^2$ tests or Student $t$ tests. Nominal $P$ values are presented. Except where noted, $P$ values <0.05 were considered statistically significant, with no adjustments made for multiple comparisons.

Linear regression models were used to evaluate the relationship of CPI, IGI, CP-iAUC/G-iAUC, and I-iAUC/G-iAUC (dependent variable) with the inverse of fasting insulin (independent variable). Models included terms to compare adults with youth and those with IGT to those with diabetes. All models used the log of β-cell response variables due to the skewedness of these data. Parallel slopes in these regression models indicate that differences in β-cell responses are proportionate across the range of insulin sensitivity.

## RESULTS

### Demographic and Physical Characteristics of Youth Versus Adults and IGT Versus Type 2 Diabetes

Table 1 lists the characteristics of youth ($n = 66$) and adult ($n = 355$) RISE participants included in this analysis. Among youth, there were fewer males and fewer white participants. Despite comparable weight, BMI and triponderal index were higher in youth than adults because they were shorter. Waist circumference, however, did not differ. Among youth participants, 78.8% were Tanner stages IV or V and 21.2% stages II or III. By protocol, no participating youth were Tanner stage I (i.e., prepubertal). Among youth, 80.3% had IGT vs. 70.7% of adults. The remainder had diabetes at screening. HbA$_{1c}$ did not differ between youth and adults.

A total of 304 participants had IGT, and 117 had type 2 diabetes (Table 1). The two groups did not differ in their racial/ethnic distribution and were well matched for physical and demographic characteristics.

### OGTT Glucose, C-Peptide, and Insulin Concentrations in Youth and Adults

The fasting glucose concentration was lower, whereas the fasting C-peptide and insulin concentrations were higher in youth compared with adults (Table 1). The mean OGTT 2-h glucose concentration was not different between youth and adults, but the 2-h C-peptide and insulin concentrations were significantly higher in youth. These differences in the 2-h C-peptide and insulin concentrations

remained significant after adjusting for differences in BMI or triponderal index, sex, and racial/ethnic distribution between youth and adults.

Figure 1A–C shows glucose, C-peptide, and insulin concentrations during the 3-h OGTT in youth and adults. Postload glucose concentrations did not differ significantly between youth and adults except for the 60-min plasma glucose, which was lower in youth (10.9 ± 2.4 vs. 11.6 ± 2.2 mmol/L; $P = 0.037$). G-iAUC did not differ between the two age-groups (Table 1). Despite these comparable OGTT glucose excursions, the C-peptide and insulin concentrations were significantly greater at all time points in youth compared with adults. These increases were reflected in the 25 and 88% greater iAUC for C-peptide and insulin, respectively (Table 1).

### OGTT Glucose, C-Peptide, and Insulin Concentrations in IGT and Type 2 Diabetes

By definition, fasting and 2-h glucose concentrations were higher in participants with recently diagnosed, drug-naïve type 2 diabetes (Table 1). Despite these differences, fasting C-peptide and insulin concentrations did not differ significantly between those with IGT and type 2 diabetes. However, both the 2-h C-peptide and insulin concentrations were significantly greater in the IGT group (Table 1).

The profiles for glucose, C-peptide, and insulin in IGT or type 2 diabetes are illustrated separately for youth (Fig. 1D–F) and adults (Fig. 1G–I). By definition, in both youth and adults, all glucose concentrations were significantly greater throughout the OGTT in those with type 2 diabetes than with IGT (all $P < 0.001$) (Fig. 1D and G and Table 2). In both youth and adults, fasting and 2-h C-peptide and insulin concentrations were not different between the glycemia groups; however, they were greater at other time points postglucose ingestion in the IGT groups ($P < 0.05$). Thus, CP-iAUC and I-iAUC were greater in IGT compared with diabetes (Table 2).

Among youth and adults with IGT, fasting glucose and HbA$_{1c}$ were lower in youth, whereas the 2-h glucose concentration and G-iAUC did not differ significantly (Table 2). Fasting and 2-h C-peptide and insulin concentrations as well as CP-iAUC and I-iAUC were greater in youth with IGT versus adults with IGT.

Among youth and adults with type 2 diabetes, fasting glucose and HbA$_{1c}$ were

greater in youth, whereas G-iAUC did not differ significantly (Table 2). Fasting C-peptide and insulin concentrations were greater in youth with type 2 diabetes, whereas the 2-h values for these peptides did not differ between the two age-groups. The iAUC for insulin was greater in youth, whereas that for C-peptide did not differ significantly between youth with type 2 diabetes and adults with type 2 diabetes.

### Insulin Sensitivity, Insulin Clearance, and β-Cell Responses in Youth and Adults

The inverse of fasting insulin, a surrogate estimate of insulin sensitivity, was 50% lower in youth compared with adults (Table 1). The lower insulin sensitivity in youth persisted after adjusting for the higher proportion of nonwhite participants, greater number of females, higher BMI, and greater triponderal index in youth. To minimize the impact of puberty-related insulin resistance at Tanner stages II–IV, an analysis that included Tanner stage V youth only ($n = 40$) was performed: insulin sensitivity was still significantly lower in youth than adults (1/FI: 5.63 ± 4.65 vs. 10.94 ± 6.41 1/[pmol/L]; $P < 0.001$).

The fasting C-peptide/insulin ratio was significantly lower in youth compared with adults (Table 1), indicative of lower insulin clearance in youth. This difference persisted after adjusting for BMI, triponderal index, sex, and racial/ethnic differences between youth and adults.

β-Cell responses determined as a function of the glucose stimulus following ingestion highlighted that the younger age-group had greater responses compared with adults, reflected by both the early C-peptide and insulin responses (CPI and IGI, respectively) and the integrated measures over the duration of the test (CP-iAUC/G-iAUC and I-iAUC/G-iAUC). The C-peptide responses in youth were 75% greater in the initial phase and 28% greater over the whole OGTT, whereas the insulin responses were about twofold greater for both time periods. These responses remained significantly greater in youth following adjustment for insulin sensitivity.

### Insulin Sensitivity, Insulin Clearance, and β-Cell Responses in IGT and Type 2 Diabetes

Comparing individuals with IGT to those with type 2 diabetes showed

**Table 1—Baseline physical characteristics, demographic characteristics, and OGTT-based measures in drug-naïve youth vs. adults and in IGT vs. type 2 diabetes**

| | Youth (n = 66) (1) | Adults (n = 355) (2) | Youth vs. adults, P value (1 vs. 2) | IGT (n = 304) (3) | Type 2 diabetes (n = 117) (4) | IGT vs. type 2 diabetes, P value (3 vs. 4) |
|---|---|---|---|---|---|---|
| **Demographic characteristics** | | | | | | |
| Age (years) | 14.2 ± 2.0 | 52.7 ± 9.4 | <0.001 | 45.7 ± 16.9 | 49.0 ± 15.1 | 0.069 |
| Male, n (%) | 19 (28.8) | 172 (48.5) | 0.005 | 140 (46.1) | 51 (43.6) | 0.730 |
| Race/ethnicity, n (%) | | | <0.001 | | | 0.197 |
|   White | 19 (28.8) | 166 (46.8) | | 140 (46.1) | 45 (38.5) | |
|   Black | 14 (21.2) | 97 (27.3) | | 83 (27.3) | 28 (23.9) | |
|   Hispanic | 25 (37.9) | 68 (19.2) | | 62 (20.4) | 31 (26.5) | |
|   Other | 8 (12.1) | 24 (6.8) | | 19 (6.2) | 13 (11.1) | |
| Weight (kg) | 98.9 ± 22.6 | 100.8 ± 18.2 | 0.454 | 101.1 ± 18.9 | 98.9 ± 19.1 | 0.281 |
| Height (cm) | 163.7 ± 9.0 | 169.2 ± 9.7 | <0.001 | 168.3 ± 9.8 | 168.4 ± 9.8 | 0.934 |
| BMI (kg/m$^2$) | 36.6 ± 6.0 | 35.1 ± 5.1 | 0.035 | 35.6 ± 5.3 | 34.8 ± 5.2 | 0.148 |
| Triponderal index (kg/m$^3$) | 22.4 ± 3.5 | 20.8 ± 3.3 | <0.001 | 21.2 ± 3.4 | 20.7 ± 3.3 | 0.166 |
| Waist circumference (cm) | 109.0 ± 14.2 | 110.3 ± 12.6 | 0.475 | 110.9 ± 13.2 | 108.3 ± 11.8 | 0.070 |
| **Glycemic characteristics** | | | | | | |
| HbA$_{1c}$ (mmol/mol) | 38.54 ± 6.11 | 39.64 ± 4.35 | 0.080 | 38.42 ± 4.11 | 42.17 ± 4.99 | <0.001 |
| Diabetes at screening, n (%) | | | 0.147 | | | — |
|   IGT | 53 (80.3) | 251 (70.7) | | — | — | |
|   Diabetes | 13 (19.7) | 104 (29.3) | | — | — | |
| **OGTT parameters** | | | | | | |
| Fasting glucose (mmol/L) | 5.93 ± 0.93 | 6.15 ± 0.65 | 0.019 | 5.94 ± 0.56 | 6.56 ± 0.84 | <0.001 |
| Fasting C-peptide (nmol/L) | 1.64 ± 0.587 | 1.24 ± 0.479 | <0.001 | 1.29 ± 0.479 | 1.34 ± 0.606 | 0.392 |
| Fasting insulin (pmol/L) | 218.2 (70.4, 676.5) | 106.4 (35.6, 318.4) | <0.001 | 120.8 (36.8, 396.7) | 115.1 (32.1, 412.6) | 0.473 |
| Two-hour glucose (mmol/L) | 9.89 ± 2.46 | 10.15 ± 2.37 | 0.404 | 9.34 ± 1.78 | 12.1 ± 2.59 | <0.001 |
| Two-hour C-peptide (nmol/L) | 5.8 ± 2.34 | 4.7 ± 1.55 | <0.001 | 5.02 ± 1.76 | 4.57 ± 1.64 | 0.018 |
| Two-hour insulin (pmol/L) | 1,418.7 (358.8, 5,608.9) | 788.8 (231.7, 2,685.5) | <0.001 | 907.1 (237.1, 3,469.5) | 764.9 (225.3, 2,597.3) | 0.020 |
| **Incremental OGTT AUC (0–180 min)** | | | | | | |
| G-iAUC (mmol/L · min) | 595.9 ± 234.9 | 613.6 ± 250.7 | 0.600 | 538.7 ± 192.4 | 794.1 ± 278.6 | <0.001 |
| CP-iAUC (nmol/L · min) | 528.7 (249.5, 1,120.1) | 424.4 (214.2, 840.7) | <0.001 | 460.4 (236.9, 894.8) | 387.8 (179.8, 836.7) | <0.001 |
| I-iAUC (pmol/L · min) | 171,453 (49,351, 595,658) | 91,284 (28,568, 291,676) | <0.001 | 108,638 (32,184, 366,705) | 82,775 (23,038, 297,408) | <0.001 |
| **Estimates of insulin sensitivity, insulin clearance, and β-cell function** | | | | | | |
| 1/FI [× 10$^{-3}$ 1/(pmol/L)] | 5.45 ± 3.88 | 10.94 ± 6.41 | <0.001 | 9.85 ± 5.96 | 10.67 ± 7.41 | 0.237 |
| Fasting C-peptide/insulin (× 10$^{-2}$ nmol/pmol) | 0.71 (0.36, 1.37) | 1.09 (0.59, 2.03) | <0.001 | 1.00 (0.50, 2.01) | 1.07 (0.53, 2.16) | 0.075 |
| CPI (nmol/mmol) | 0.703 (0.226, 2.183) | 0.401 (0.136, 1.183) | <0.001 | 0.508 (0.171, 1.51) | 0.297 (0.111, 0.796) | <0.001 |
| IGI (pmol/mmol) | 257.3 (54.5, 1,215.8) | 114.8 (28.0, 470.8) | <0.001 | 154.1 (34.1, 697.4) | 84.7 (23, 311.9) | <0.001 |
| CP-iAUC/G-iAUC (nmol/mmol) | 0.972 (0.332, 2.846) | 0.762 (0.261, 2.218) | 0.001 | 0.927 (0.368, 2.335) | 0.526 (0.184, 1.505) | <0.001 |
| I-iAUC/G-iAUC (pmol/mmol) | 312.6 (72.7, 1,343.3) | 163.9 (40.9, 657.0) | <0.001 | 218.7 (58.7, 814.4) | 112.3 (26.8, 470.1) | <0.001 |

Data are mean ± SD or geometric mean (95% CI). P values for nonnormally distributed data based on log-transformed values. "Other" for self-reported race/ethnicity includes, mixed, Asian, American Indian, and other.

no difference in insulin sensitivity (1/FI; Table 1). However, all β-cell responses (CPI, IGI, CP-iAUC/G-iAUC, and I-iAUC/G-iAUC) were significantly lower in the group with type 2 diabetes. In contrast with the observation in youth versus adults, insulin clearance was not different between those with IGT versus diabetes.

Further analysis of those with IGT or type 2 diabetes among youth and adults separately yielded some differences (Table 2). In both IGT and type 2 diabetes, the inverse of fasting insulin was ∼50% lower in youth compared with adults. Early phase C-peptide and insulin responses were significantly greater in youth with either IGT or type 2 diabetes, although

relative differences were smaller in those with diabetes (CPI: 77% higher in youth than adults with IGT and 34% higher in youth than adults with diabetes; IGI: 126% higher in youth than adults with IGT and 68% higher in youth than adults with diabetes). Similar patterns were observed for β-cell responses over the whole OGTT (CP-iAUC/G-iAUC and
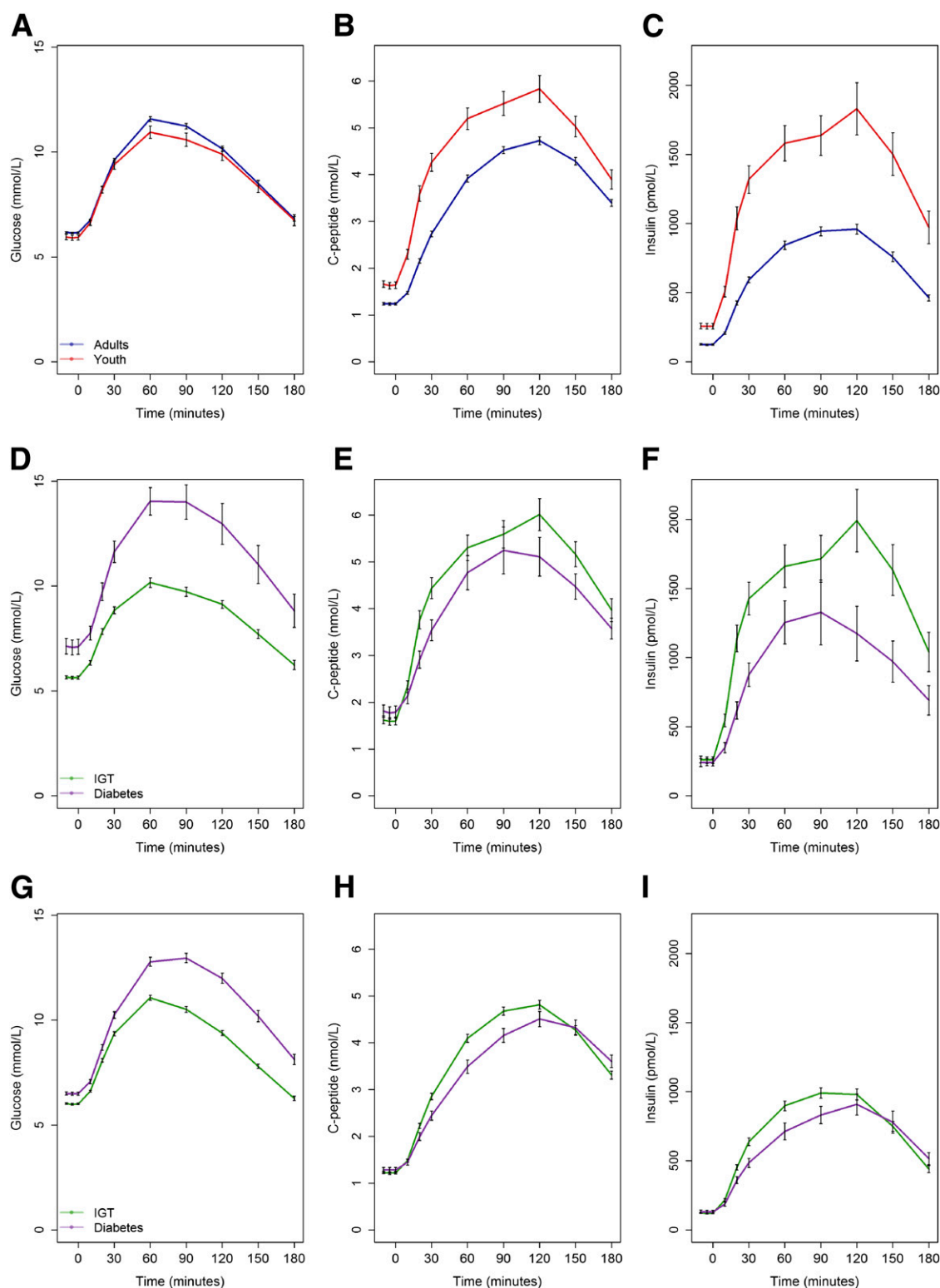
**Figure 1**—Plasma glucose, C-peptide, and insulin concentrations during the OGTT in youth and adults (*A–C*), youth with IGT and diabetes (*D–F*), and adults with IGT and diabetes (*G–I*). Youth are shown in red, adults in blue, IGT in green, and diabetes in purple. Data are mean ± SEM. In youth and adults, at all time points following glucose ingestion, glucose concentrations were similar except at 60 min ($P = 0.037$). C-peptide and insulin were greater in youth at all time points ($P \leq 0.009$). In IGT and diabetes, in both youth and adults, the glucose values were greater in diabetes compared with IGT (all $P < 0.001$). In youth, although the differences were large, they only reached significance at 20 min for C-peptide ($P = 0.040$) and 10–30 min for insulin ($P < 0.05$). In adults, both C-peptide and insulin were greater in IGT from 20 to 90 min ($P < 0.05$).

I-iAUC/G-iAUC), but in this instance, only the C-peptide and insulin responses in youth and adults with IGT differed significantly.

### Relationship of Insulin Sensitivity to C-Peptide and Insulin Responses in Youth and Adults and in IGT and Diabetes

The relationships of insulin sensitivity with CPI and IGI for youth and adults are depicted in Fig. 2A and B. Both CPI and IGI were inversely related to insulin sensitivity; although the slopes in youth and adults did not differ ($P = 0.577$ and $P = 0.563$, respectively), both CPI and IGI were significantly higher at a given level of insulin sensitivity in youth than in adults (both $P < 0.001$).

When participants were categorized based on glucose tolerance status (IGT and diabetes) (Fig. 2C and D), the difference in the slopes relating insulin sensitivity to CPI in IGT versus diabetes approached significance ($P = 0.074$), whereas that relating insulin sensitivity to IGI was significant ($P = 0.007$). CPI and IGI were both lower in diabetes than IGT at a given level of insulin sensitivity (both $P < 0.001$). Thus, across the range of insulin sensitivity, CPI and IGI were greater in those with IGT compared with type 2 diabetes, although this difference decreased with increasing insulin sensitivity.

Similar relationships existed between insulin sensitivity and the β-cell responses measured over the 3 h of the test (CP-iAUC/G-iAUC and I-iAUC/G-iAUC) in youth and adults as well as IGT and diabetes (Supplementary Fig. 1).

### Determinants of the OGTT 2-h Glucose Concentration and Glucose Excursion

To assess the relative importance of insulin sensitivity and/or β-cell responses in determining glucose tolerance, we examined the relationships of 1/FI, CPI, and IGI with the 2-h glucose concentration (Fig. 3A–C). Insulin sensitivity was not related to the 2-h glucose concentration in either youth ($r = -0.11$; $P = 0.373$) or adults ($r = -0.039$; $P = 0.456$) (Fig. 3A). In contrast, both CPI (youth: $r = -0.50$, $P < 0.001$; adults: $r = -0.47$, $P < 0.001$) and IGI (youth: $r = -0.37$, $P = 0.003$; adults: $r = -0.37$, $P < 0.001$) were inversely related to the 2-h glucose concentration (Fig. 3B and C). Although the slopes for youth and adults were not significantly different for the relationship between the 2-h glucose and CPI or IGI, youth had higher peptide

responses than adults for both CPI ($P = 0.004$) and IGI ($P = 0.034$) across the range of 2-h glucose concentration.

Similarly, total glucose excursion during the OGTT (G-iAUC) was not related to insulin sensitivity in youth or adults (youth: $r = -0.015$, $P = 0.90$; adults: $r = 0.014$, $P = 0.79$) (Fig. 3D). In contrast, G-iAUC was related to early β-cell responses (CPI in youth: $r = -0.506$, $P < 0.001$ and adults: $r = -0.500$, $P < 0.001$; IGI in youth: $r = -0.400$, $P = 0.001$ and adults: $r = -0.400$, $P < 0.001$) (Fig. 3E and F). Slopes relating G-iAUC and CPI and IGI were not different between youth and adults; however, again youth had higher peptide responses for CPI ($P < 0.001$) and IGI ($P = 0.009$) across the range of total glucose excursion.

## CONCLUSIONS

The pathogenesis of type 2 diabetes in both youth and adults involves dual defects: insulin resistance and β-cell dysfunction (14–16). We have used OGTT data from the RISE Study to perform direct comparisons between youth and adults using shared measurement methodologies. Following glucose ingestion, youth exhibited higher C-peptide and insulin responses despite matched glucose excursions. These increased C-peptide and insulin responses in youth exceeded what would be needed to compensate for their markedly lower insulin sensitivity. Further, these OGTT data not only mirror what we observed using the hyperglycemic clamp (5), but also demonstrate that this effect is also present in response to physiologic delivery of glucose. This suggests that in youth, this hyperresponsiveness is occurring with food intake every day. With these analyses, we have also extended the clamp observations by demonstrating that the β-cell change responsible for the hyperresponsiveness in youth is lost with disease progression.

The differences observed in β-cell responsiveness between the two age-groups and the difference in responses within glucose tolerance categories are novel. Not only did we observe the expected inverse relationship between insulin sensitivity and β-cell responses (9), but also an enhancement of the β-cell responses in youth across the range of insulin sensitivity in keeping with it not simply being due to the difference in

insulin sensitivity. Further, the lack of a difference in glucose concentrations between groups during the OGTT argues that glucose is not mediating this effect. As we also observed increased β-cell responsiveness in these youth with intravenous administration of glucose and the nonglucose secretagogue arginine (5), this effect seems to be generalized rather than specific to a secretagogue or route of administration. Importantly, the current observations using oral glucose delivery support the assumption that this hyperresponsiveness is occurring in youth in response to all nutrients on a daily basis. Among the possible explanations for this enhanced responsiveness are: 1) increased circulating incretins or β-cell sensitivity to these peptides, 2) genetic defects or epigenetic changes resulting in hyperresponsiveness, and/or 3) altered central regulation resulting in increased parasympathetic/vagal tone and insulin secretion. In the latter two instances, it is possible that a primary β-cell lesion resulting in hypersecretion will also lead to peripheral downregulation of insulin action to avoid hypoglycemia (17). Further research will be needed to explore these possibilities.

The C-peptide and insulin responses in youth with IGT were significantly greater than in adults in both the early responses and total response over the 3-h test. Among those with diabetes, the early responses were also greater in youth, but this was not the case over the entire test for either C-peptide or insulin. Thus, the ratio of each β-cell response in youth to adults was less in those with diabetes than IGT (diabetes vs. IGT, respectively; CPI: 1.34- vs. 1.77-fold; IGI: 1.68- vs. 2.26-fold; CP-iAUC/G-iAUC: 1.02- vs. 1.26-fold; and I-iAUC/G-iAUC 1.42- vs. 1.92-fold). This mirrors our observations with the clamp studies, in which youth had greater differences compared with adults in the acute (first-phase) response to intravenous glucose than in the steady-state (second-phase) response (5). Our observation of differences in the magnitude and nature of the β-cell responses by age and category of glucose tolerance are also consistent with a recent report that used mathematical modeling of OGTT data obtained from pooled studies (18).

We observed 50% lower insulin sensitivity in youth using the inverse of fasting insulin. This difference is similar to the 46% reduction in insulin sensitivity

**Table 2—OGTT-based measures in drug-naïve youth and adults subdivided based on glucose tolerance category (IGT vs. type 2 diabetes)**

| Characteristic | Youth (n = 66) IGT (n = 53) (1) | Youth Type 2 diabetes (n = 13) (2) | P value (1 vs. 2) | Adults (n = 355) IGT (n = 251) (3) | Adults Type 2 diabetes (n = 104) (4) | P value (3 vs. 4) | Youth IGT vs. adults IGT, P value (1 vs. 3) | Youth with type 2 diabetes vs. adults with type 2 diabetes, P value (2 vs. 4) |
|---|---|---|---|---|---|---|---|---|
| **Glycemic characteristic** | | | | | | | | |
| HbA$_{1c}$ (mmol/mol) | 36.78 ± 4.57 | 45.70 ± 6.52 | <0.001 | 38.77 ± 3.93 | 41.73 ± 4.62 | <0.001 | 0.001 | 0.006 |
| **OGTT parameters** | | | | | | | | |
| Fasting glucose (mmol/L) | 5.64 ± 0.53 | 7.10 ± 1.29 | <0.001 | 6.01 ± 0.55 | 6.5 ± 0.75 | <0.001 | <0.001 | 0.014 |
| Fasting C-peptide (nmol/L) | 1.601 ± 0.608 | 1.791 ± 0.483 | 0.299 | 1.223 ± 0.420 | 1.281 ± 0.598 | 0.303 | <0.001 | 0.004 |
| Fasting insulin (pmol/L) | 215.9 (63.9, 729.4) | 227.7 (111.9, 463.4) | 0.768 | 106.8 (37.9, 300.6) | 105.6 (30.7, 363) | 0.870 | <0.001 | 0.002 |
| Two-hour glucose (mmol/L) | 9.13 ± 1.34 | 12.97 ± 3.51 | <0.001 | 9.39 ± 1.86 | 11.99 ± 2.45 | <0.001 | 0.202 | 0.338 |
| Two-hour C-peptide (nmol/L) | 6.01 ± 2.48 | 5.11 ± 1.5 | 0.216 | 4.81 ± 1.5 | 4.51 ± 1.65 | 0.089 | <0.001 | 0.214 |
| Two-hour insulin (pmol/L) | 1,527.5 (362.1, 6,444.3) | 1,049.8 (432.9, 2,545.8) | 0.084 | 812.2 (240.5, 2,742.6) | 735.2 (212.8, 2,540) | 0.173 | <0.001 | 0.248 |
| **Incremental OGTT AUC (0–180 min)** | | | | | | | | |
| G-iAUC (mmol/L · min) | 528.9 ± 164.4 | 858.8 ± 288.2 | <0.001 | 540.7 ± 197.9 | 786 ± 277.8 | <0.001 | 0.377 | 0.377 |
| CP-iAUC (nmol/L · min) | 555 (258.4, 1,192.1) | 429.8 (248.7, 742.9) | 0.036 | 442.9 (239.0, 820.7) | 383.2 (174.0, 843.8) | <0.001 | 0.339 | 0.339 |
| I-iAUC (pmol/L · min) | 185,932 (51,812, 667,233) | 124,745 (50,683, 307,030) | 0.042 | 97,185 (32,857, 287,458) | 78,599 (21,703, 284,646) | 0.002 | 0.016 | 0.016 |
| **Estimates of insulin sensitivity, insulin clearance, and β-cell function** | | | | | | | | |
| 1/FI × [10$^{-3}$ 1/(pmol/L)] | 5.65 ± 4.25 | 4.65 ± 1.56 | 0.408 | 10.74 ± 5.89 | 11.43 ± 7.52 | 0.359 | <0.001 | <0.001 |
| Fasting C-peptide/insulin (× 10$^{-2}$ nmol/pmol) | 0.69 | 0.76 | 0.373 | 1.08 | 1.12 | 0.356 | <0.001 | <0.001 |
| CPI (nmol/mmol) | 0.815 (0.293, 2.263) | 0.385 (0.183, 0.81) | <0.001 | 0.46 (0.169, 1.248) | 0.287 (0.106, 0.779) | <0.001 | <0.001 | 0.048 |
| IGI (pmol/mmol) | 301.8 (66.8, 1,363.4) | 134.4 (49.0, 368.8) | <0.001 | 133.4 (34.4, 516.4) | 79.8 (21.9, 291.7) | <0.001 | <0.001 | 0.007 |
| CP-iAUC/G-iAUC (nmol/mmol) | 1.119 (0.447, 2.798) | 0.536 (0.214, 1.343) | <0.001 | 0.891 (0.359, 2.211) | 0.525 (0.18, 1.529) | <0.001 | 0.002 | 0.897 |
| I-iAUC/G-iAUC (pmol/mmol) | 374.7 (102.4, 1,370.4) | 153.5 (44.9, 525) | <0.001 | 195.6 (58.3, 656.3) | 108 (25.5, 456.8) | <0.001 | <0.001 | 0.102 |

Data are mean ± SD or geometric mean (95% CI). P values for nonnormally distributed data based on log-transformed values.
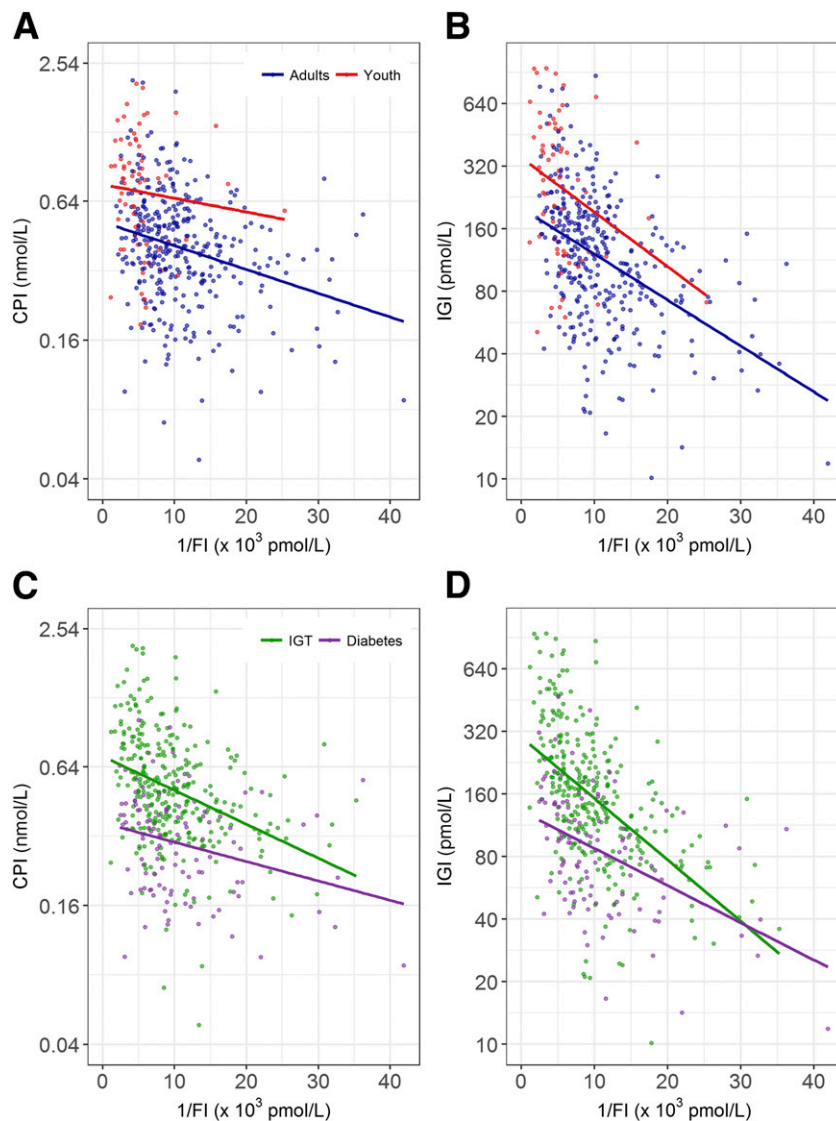
**Figure 2**—Relationship of insulin sensitivity (1/FI) with the CPI and IGI from the OGTT in youth and adults (A and B, respectively) and those with IGT and diabetes (C and D, respectively). Youth are shown in red, adults in blue, IGT in green, and diabetes in purple. CPI and IGI are presented on a log scale. The slopes relating early β-cell response measures to insulin sensitivity were all significant ($P < 0.001$), and the group differences were all significant (youth vs. adults: $P < 0.001$ for CPI and IGI; IGT vs. diabetes: $P < 0.001$ for CPI and IGI). The slopes for youth and adults did not differ ($P = 0.577$ for CPI and $P = 0.563$ for IGI), whereas in IGT and diabetes, that for CPI did not differ ($P = 0.074$) but for IGI did ($P = 0.007$).

we quantified using the hyperglycemic clamp (5) and results from two recent retrospective analyses of cohorts studied for other purposes (18,19). The basis for the lower insulin sensitivity in youth in RISE does not seem to be due simply to dissimilarities in sex (20,21), race/ethnicity (14,22), or body size (23) that are known to affect insulin sensitivity, as this difference persisted in our data after accounting for any potential effect of these differences. Consistent with our findings, when obese youth with IGT were matched for BMI, sex, and race to adults with IGT, youth exhibited 40–50% lower peripheral and

hepatic insulin sensitivity, twofold higher fasting insulin concentrations, and lower insulin clearance compared with adults (19). Although physiological transition through puberty is known to reduce insulin sensitivity, it returns to near prepubertal levels once puberty is complete (24–26). However, a difference in insulin sensitivity was still present when we limited the comparator group to youth at Tanner stage V, which is postpubertal and more akin to adulthood. Our findings may differ from previous studies, however, as studies of pubertal insulin resistance have been performed in normal weight

youth or those across a wide spectrum of weight/BMI and not specifically in obese youth. It is also possible that as obese prepubertal youth transition through puberty, they might sustain a greater decrease in insulin sensitivity consequent to the combined effect of puberty and obesity. Also, it remains unknown if their puberty-related insulin resistance recovers with completion of puberty. We did not collect data on other factors that could affect insulin sensitivity, which include environmental factors such as nutrient balance (27), exercise (28), and stress (29) as well as physiological factors such as menstrual status (30) and body fat topography (31); therefore, we cannot determine whether these or other unmeasured factors are contributing to the observed differences. Finally, whether a unique genetic component(s) could also be causative cannot be excluded.

Type 2 diabetes appears to be more aggressive in youth, with a faster rate of deterioration of β-cell function (32) and poorer response to glucose-lowering medications (33). Our observation of a smaller relative difference in the C-peptide and insulin responses between youth and adults with diabetes versus those with IGT suggests that the β-cell change responsible for the hyperresponsiveness in youth is lost with disease progression from IGT to type 2 diabetes. It also suggests the possibility that the deterioration in β-cell function that occurs with progression from IGT to diabetes is greater, more rapid, and/or may also continue beyond the time of diabetes diagnosis. Such a difference could possibly also explain why type 2 diabetes presents at an earlier age and the response to glucose-lowering therapy is poorer so that hyperglycemia appears to progress more rapidly in youth (33,34). Although studies have demonstrated the possibility to preserve β-cell function in adults with IGT or recent-onset type 2 diabetes (35,36), future longitudinal and intervention studies, including the results of the RISE Study evaluating the effects of β-cell rest in this cohort of youth, will be needed to define and provide greater insight into these distinctions between the two age-groups.

In our data in both youth and adults, the β-cell's early response (CPI and IGI) was a more important determinant of the 2-h glucose concentration than insulin sensitivity. Also, the early β-cell response in youth was greater than adults across the achieved 2-h glucose concentration
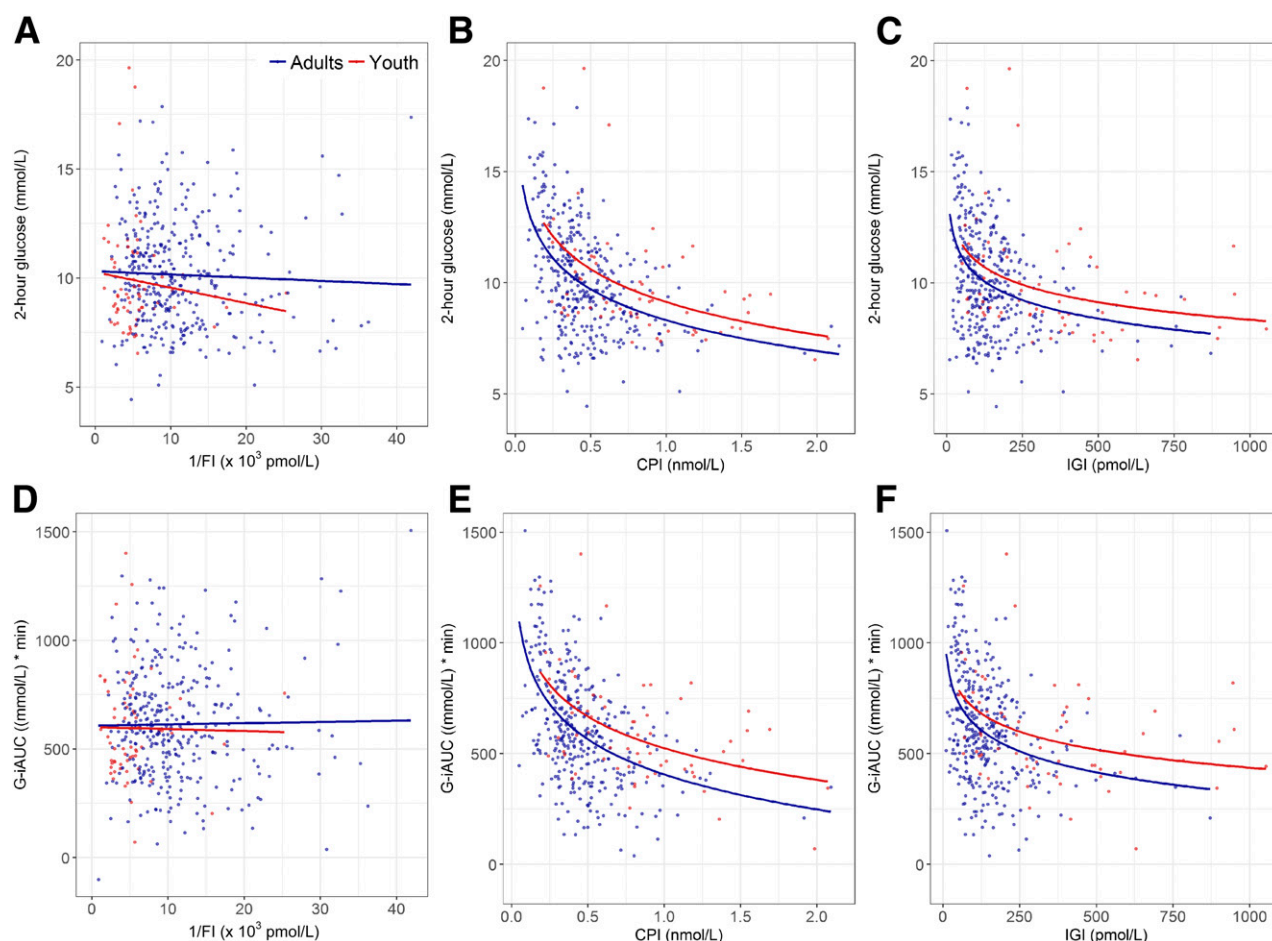
**Figure 3**—Relationship in youth and adults of the OGTT 2-h glucose concentration (*A–C*) and glucose excursion determined as G-iAUC (*D–F*) with insulin sensitivity (1/FI; *A* and *D*), CPI (*B* and *E*), and IGI (*C* and *F*), respectively. Youth are shown in red and adults in blue. The slopes relating the 2-h glucose concentration and G-iAUC to insulin sensitivity were not significant in youth or adults ($P$ = 0.373–0.900). For calculation of the slopes relating the 2-h glucose concentration and G-iAUC to CPI and IGI, the β-cell responses were log transformed. Slopes relating the 2-h glucose concentration to CPI and IGI were all significant ($P < 0.001$ for youth and adults for CPI and adults for IGI; $P$ = 0.003 for youth for IGI), and the group differences were significant ($P$ = 0.004 for CPI and $P$ = 0.034 for IGI). Slopes relating G-iAUC to CPI and IGI were all significant ($P < 0.001$ for youth and adults for CPI and adults for IGI; $P$ = 0.001 for youth for IGI), and the group differences were significant ($P < 0.001$ for CPI and $P$ = 0.009 for IGI). For the 2-h glucose, the slopes for youth and adults did not differ ($P$ = 0.476 for 1/FI; $P$ = 0.806 for CPI; and $P$ = 0.852 for IGI). Likewise, for G-iAUC, the slopes for youth and adults did not differ ($P$ = 0.858 for 1/FI; $P$ = 0.665 for CPI; and $P$ = 0.623 for IGI).

and the indices of total glucose excursion. These observations are in line with a previous report of OGTT data in 531 first-degree relatives of individuals from four different ethnic groups with normal glucose tolerance, IGT, and newly identified diabetes, which found that the early insulin response explained threefold more of the variance in the 2-h glucose concentration than did insulin sensitivity measured as HOMA of insulin resistance (14).

There are limitations to the current analyses. Our comparisons are cross-sectional, and it is unclear whether observed differences between youth and adults represent underlying group differences or transient differences that will resolve with maturation. Because most of the youth had completed puberty in Tanner stage V, it is unlikely that the observed differences are due to puberty, as discussed above in detail. Longitudinal studies that include youth with normal glucose tolerance, IGT, and type 2 diabetes are needed to evaluate temporal changes in β-cell hyperresponsiveness with maturation. The current findings are based on a relatively small number of youth who had diabetes and were drug naïve. Further, they differed from adults in sex and race/ethnicity distribution, both of which were adjusted for in our analyses. Nevertheless, we saw noteworthy group differences between youth and adults.

In conclusion, this analysis of OGTT data from RISE highlights the fundamental differences in insulin sensitivity and β-cell function in youth and adults with IGT and recently diagnosed, drug-naïve type 2 diabetes. These data complement parallel analyses in the same cohort using clamp studies and underscore the likely relevance of these phenomena to daily meal ingestion. The observed hyperresponsiveness of β-cells may be a critical factor in the observed accelerated progression to diabetes at a young age and youth's more aggressive disease.

## Appendix

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