Comparison of β-Cell Function Between Overweight/Obese Adults and Adolescents Across the Spectrum of Glycemia

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OBJECTIVE

Type 2 diabetes is a growing health problem among both adults and adolescents. To better understand the differences in the pathogenesis of diabetes between these groups, we examined differences in β-cell function along the spectrum of glucose tolerance.

RESEARCH DESIGN AND METHODS

We evaluated 89 adults and 50 adolescents with normal glucose tolerance (NGT), dysglycemia, or type 2 diabetes. Oral glucose tolerance test results were used for C-peptide and insulin/glucose minimal modeling. Model-derived and direct measures of insulin secretion and insulin sensitivity were compared across glycemic stages and between age-groups at each stage.

RESULTS

In adolescents with dysglycemia, there was marked insulin resistance (insulin sensitivity index: adolescents, median [interquartile range] 1.8 [1.1–2.4] × 10^{-4}; adults, 5.0 [2.3–9.9]; *P* = 0.01). The nature of β-cell dysfunction across stages of dysglycemia differed between the groups. We observed higher levels of secretion among adolescents than adults (total insulin secretion: NGT, 143 [103–284] × 10^{-9}/min adolescent vs. 106 [71–127], *P* = 0.001); adults showed stepwise impairments in static insulin secretion (NGT, 7.5 [4.0–10.3] × 10^{-9}/min; dysglycemia, 5.0 [2.3–9.9]; type 2 diabetes, 0.7 [0.1–2.45]; *P* = 0.003), whereas adolescents showed diabetes-related impairment in dynamic secretion (NGT, 1,905 [1,630–3,913] × 10^{-9}; dysglycemia, 2,703 [1,323–3,637]; type 2 diabetes, 1,189 [269–1,410]; *P* = 0.001).

CONCLUSIONS

Adults and adolescents differ in the underlying defects leading to dysglycemia, and in the nature of β-cell dysfunction across stages of dysglycemia. These results may suggest different approaches to diabetes prevention in youths versus adults.

The progression from normal glucose tolerance (NGT) through dysglycemia (impaired fasting and/or impaired glucose tolerance [IGT]) to type 2 diabetes is marked by concurrent changes in insulin sensitivity and β-cell function (i.e., insulin secretion). Models based on longitudinal data suggest that changes in insulin sensitivity dominate the transition from NGT to dysglycemia, whereas changes in β-cell function drive the transition from dysglycemia to overt diabetes (1). These components are interdependent, with the magnitude of insulin secretion determined in part by the ambient insulin sensitivity. This interdependence is captured by the disposition index (DI), a numerical product of the

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two parameters, which aids in distinguishing appropriate compensatory changes from insufficient compensation (2). DIs have been constructed from direct measures of insulin secretion and insulin sensitivity (e.g., using glucose clamp methodology) or from measures derived from mathematical models based on biochemical excursions after intravenous or oral glucose loading (3).

In adolescent type 2 diabetes, alarming trends in clinical progression and outcomes have been recently observed, in particular what appears to be markedly more aggressive disease progression compared with a more indolent and gradual process among adults (4–6). Variations in the balance of β-cell dysfunction and insulin resistance (IR) that underlie states of dysglycemia have been described in adult populations (7–9) and in the growing population of pediatric participants at risk for, or with, type 2 diabetes (10–12). Puberty-related IR is a β-cell stressor exclusive to adolescents, which may produce unique patterns in the pathogenesis and advance of dysglycemia.

These observations call for a better understanding of the pathogenesis of dysglycemia and how it might differ between youths and adults. There are very few data providing direct comparisons of adults and youths across the spectrum of glycemia. Here we have undertaken comparisons of overweight or obese adults and youths with normoglycemia, dysglycemia (impaired fasting glucose or IGT), and type 2 diabetes using standardized oral glucose tolerance testing and mathematical modeling to derive detailed phenotypes of β-cell function. We hypothesized that obese youths and adults would show informative differences in the pattern of β-cell dysfunction across the clinical spectrum of glucose tolerance. These efforts provide key information that may help guide us toward more effective age-specific treatment or prevention interventions.

RESEARCH DESIGN AND METHODS

Participants

We analyzed data from physiologic studies performed at Indiana University from 2009 through 2012, some portions of which have been previously published (13–16). The individual studies and the aggregation of study data into a cross-sectional data set for analyses such as those presented here were approved by the institutional review board at Indiana University. Written informed consent was obtained from all participants, including approval for the use of their data in analyses unrelated to the primary study.

Pubertal adolescents ≤18 years of age with a BMI >95th percentile for age and sex presented for the evaluation and treatment of obesity at a tertiary care specialty clinic and were offered an opportunity to participate; the youngest age of our participants was 12 years. Tanner staging was performed clinically as part of those visits. Individuals with syndromic obesity, chronic disease, or long-term medication use interfering with endocrine function or glucose regulation were excluded. Diabetes status was determined by prior physician diagnosis or was defined with protocol testing using a 2-h 75-g oral glucose tolerance test (OGTT) performed under fasting conditions (detailed below), applying the American Diabetes Association criteria of fasting glucose level >126 mg/dL or 2-h glucose level >200 mg/dL.

Adult subjects presented for participation in ongoing clinical studies of glucose metabolism, with inclusion criteria of age >18 years, nonpregnant, nonsmoker, with no chronic illnesses or use of medications that affect glucose metabolism. The current analyses included only overweight or obese individuals (BMI >25 kg/m^2). Adult BMI *z* scores were assigned using 2012 National Health and Nutrition Examination Survey data on the national distribution of BMI values. Diabetes was determined as described above, using clinical diagnoses or data from the OGTT performed under the study protocols. Participants with diabetes were excluded if they had been treated with a thiazolidinedione within 6 months of the planned measurements (given the sustained effects of these agents to alter the endogenous metabolic balance) or if their fasting glucose level on the morning of the planned glucose tolerance test exceeded 300 mg/dL (to mitigate the risk of marked hyperglycemia after glucose ingestion). In both populations, oral antidiabetic medications were withheld for a minimum of 24 h or three half-lives prior to glucose tolerance testing. No insulin-treated participants were studied.

Procedures

Study procedures for adolescents were performed at the Indiana Clinical and Translational Sciences Institute Clinical Research Center after an overnight fast. Age was determined to the nearest year; weight and height were determined to the nearest 0.1 kg and 0.1 cm, respectively; and resting blood pressure was measured with an anaeroid sphygmomanometer on the upper arm using an appropriately sized cuff. Fasting blood was sampled for measurement of fasting insulin, C-peptide, glucose, and other analytes. Next, a standard 75-g OGTT was performed, with serum glucose, insulin, and C-peptide sampled at times −15, 0, 15, 30, 60, 90, and 120 min.

Study procedures for adults were also performed at the Indiana Clinical and Translational Sciences Institute Clinical Research Center after an overnight fast. The procedures performed paralleled those for the adolescents, except that the timing for the sampling with the 75-g OGTT differed, with sampling at times of −15, 0, 10, 20, 30, 60, 90, 120, and 180 min. These differences in timing arose as a result of differences in the original protocols contributing data.

Fasting lipids and liver enzymes were performed in the Indiana University Health Pathology Laboratory using standard methodologies for all subjects. Glucose measurements were performed at the bedside using a glucose oxidase method (within-run CV 2%) (YSI 2700 STAT Glucose Analyzer; Yellow Springs Instruments, Yellow Springs, OH). The Indiana Diabetes Research Center Translation Core performed measurements of glucose (pediatric participants; glucose oxidase method) (RX Daytona; Randox, Crumlin, U.K.; CV 4.5%), insulin (radioimmunoassay; Millipore/Linco, St. Charles, MO; intra-assay CV 2.2–4.4%), and C-peptide (radioimmunoassay; Millipore/Linco; intra-assay CV 3.4–6.4%).

Assessment of β-Cell Function

Direct Measures

We calculated traditional measures of insulin secretion and IR from the OGTT data, including the homeostasis model IR index HOMA-IR, insulinogenic index (IGI $[(Ins_{30} - Ins_0)/(Gluc_{30} - Gluc_0)]$), and C-peptide index (CPI $[(Cpep_{30} - Cpep_0)/(Gluc_{30} - Gluc_0)]$).

Model-Derived Measures

Insulin sensitivity was estimated using the oral insulin/glucose minimal model, while insulin secretion measures were derived from the oral C-peptide minimal model, both using SAAM II software (version 2.3.1.1; The Epsilon Group, Charlottesville, VA). The oral minimal model is based on a single-compartment system with a

single input via the ingested glucose dose, modeling a monophasic glucose time course (3). This modeling approach has been extensively validated and is arguably preferable over simpler approaches to measurement of β-cell function, as reviewed by Cobelli et al. (3). In a minority of cases, the experimental data exhibited nonmonophasic glucose curves, typically failing to fall monotonically over the late interval of observation. Such data proved difficult to model. Therefore, if a second rise in glucose, defined as an increase >4.5 mg/dL above a previous nadir (17–19), was evident, we truncated the modeled experiment length to capture the first rise and fall of glucose as monophasic. In these instances and where otherwise necessary, modeling equations were adjusted as previously described (20) for variations in sampling times and experiment lengths. Measured glucose, insulin, and C-peptide concentrations during 2- and 3-h OGTT for adolescents and adults, respectively, were used as the known input, and glucose derivatives were calculated using MATLAB software (R2016a, version 9.0.0.341360; MathWorks, Natick, MA). All baseline inputs (gss, Ib, Cpb) were taken as the mean of measured values at $t = -15$ and $t = 0$. Where $t = -15$ data were missing, data points at $t = 0$ were taken as the basal value (21). Area under the curve for glucose was calculated using the trapezoidal equation. Body volume used in the C-peptide model was calculated, and C-peptide kinetic parameters FRA and A1 were designated as previously described (22).

These models produced estimates for each participant of Si (the insulin sensitivity index), Φd (dynamic insulin secretion; reflecting changes in secretion in response to immediate changes in glucose), Φs (static insulin secretion; reflecting insulin secretion distinct from the dynamic response), and Φt (total insulin secretion; incorporating both Φs and Φd) (3,23). DIs were then calculated from these measurements by combining modeled Φ with modeled Si (3).

Statistics

Statistical analyses were performed using SPSS software (version 24.0; IBM, Armonk, NY). All data were presented as the mean ± SD, where applicable. Patient characteristics were compared using χ^2 analyses and one-way ANOVA as appropriate. The adolescent BMI was further expressed as the BMI SD score, and adolescent blood pressure was expressed as the percentile per norms for age, sex, and height (24). Patients were characterized as being normal, having dysglycemia (IGT; 2-h glucose >140 mg/dL or impaired fasting glucose; fasting glucose >100 mg/dL), or having type 2 diabetes (pre-existing diagnosis or by study OGTT using American Diabetes Association glucose criteria) (25). Measures of β-cell function and insulin sensitivity were compared within and between each age category using one- and two-way ANOVA. Non-normally distributed parameters were log transformed before analysis; data are presented as nontransformed values for clarity. Additionally, because the groups differed significantly by obesity measures despite the exclusion of lean individuals, all analyses presented included an adjustment for BMI *z* score. Parallel analyses were also performed adjusting for BMI directly, without material differences in the overall pattern of significant differences (data not shown).

The primary comparison of interest was the interaction of age and glycemic category, asking whether the pattern of change across glycemic categories differed between adults and adolescents. $P \leq 0.05$ was considered statistically significant.

RESULTS

Patient Characteristics

Eighty-nine overweight and obese adults (BMI 31.5 ± 6.7 kg/m^2 [mean ± SD]; 39.6% female) 47.1 ± 10.4 years of age (age range 26–66 years) and 50 obese adolescents (BMI 39.0 ± 8.2 kg/m^2, 52% female) 14.4 ± 1.7 years of age (age range 12–18 years) with sufficient data for at least one minimal model were included. Sensitivity analyses incorporating sex or ethnicity as covariates did not meaningfully alter the results. Consequently, the results that follow are not adjusted for sex or ethnicity. As described above, all between-group comparisons were adjusted for BMI *z* scores owing to the different degrees of obesity in the adult and adolescent cohorts.

Data from 81 adults and 43 adolescents were available for paired C-peptide and insulin/glucose minimal modeling, allowing the calculation of model-derived DIs in these individuals. The anthropometric and metabolic characteristics of this majority subset did not differ from the complete group (data not shown).

Patient characteristics are summarized in Table 1. Adolescents with NGT and dysglycemia had higher BMI and BMI *z* scores compared with adults at similar clinical stages. Adolescents with NGT and dysglycemia also had higher fasting insulin concentrations than adults at the same clinical stage, whereas youths with diabetes had lower HbA_{1c} levels than adults with diabetes. Adolescents had lower total cholesterol than adults at all stages, but adolescents with dysglycemia also had higher triglyceride and lower HDL levels than adults with dysglycemia. The mean systolic and diastolic blood pressure percentiles were higher in adolescents with dysglycemia than in those with normoglycemia (systolic blood pressure $P = 0.001$; diastolic blood pressure $P = 0.005$) but were not different between youths with dysglycemia and those with type 2 diabetes. Systolic blood pressure was significantly higher in adults with diabetes than in those with dysglycemia ($P = 0.047$), but systolic and diastolic blood pressure did not otherwise differ between adult categories.

Differences Across Glycemic Stages

Measures of β-cell function and insulin sensitivity are presented in Figs. 1 and 2 and Table 2. Statistical comparisons of these measures were adjusted for BMI *z* score. In the overweight and obese adults studied, measures of insulin sensitivity did not differ between normoglycemic individuals and those with dysglycemia. In adults with type 2 diabetes, however, Si was lower and HOMA-IR higher than in normoglycemic subjects or subjects with dysglycemia (all $P < 0.001$). The β-cell function measures IGI and CPI, and their respective DIs, showed stepwise decreases across worsening clinical stages (NGT vs. dysglycemia $P < 0.05$; NGT vs. diabetes, and dysglycemia vs. diabetes, all $P < 0.001$). Model-derived measures followed a parallel pattern, as follows: Φt was lower in each successive clinical stage (NGT vs. dysglycemia $P = 0.029$; NGT vs. diabetes $P < 0.001$; dysglycemia vs. diabetes $P < 0.001$), which is attributable primarily to a decreased static component of insulin secretion (Φs) across stages (NGT vs. dysglycemia $P = 0.033$; NGT vs. diabetes $P < 0.001$; dysglycemia vs. diabetes $P < 0.001$). The DIs calculated from these parameters showed similar steps across glycemic stages (DI-Φt NGT vs. dysglycemia $P = 0.013$; NGT vs. diabetes $P < 0.001$; dysglycemia vs. diabetes

Table 1—Characteristics of adults and adolescents at each clinical stage

	Adults (n = 89)			Adolescents (n = 50)			P value		
Age, mean ± SD (range)	46.1 ± 10.3 (26–66)			14.4 ± 1.7 (12–18)					
Sex (M/F), n	52/37			24 /26				0.15	
Race (AW/AA), n	34/55			27/22				0.62	
Clinical stage	Normoglycemic (n = 30)	Dysglycemic (n = 36)	Type 2 diabetes (n = 23)	Normoglycemic (n = 33)	Dysglycemic (n = 11)	Type 2 diabetes (n = 6)	Age	Stage	Age*Stage
Tanner stage, n (%)									
II				1 (3.3)	0 (0)	1 (16.7)			
III				9 (27.3)	1 (9.1)	0			
IV				5 (15.2)	3 (27.3)	2 (33.3)			
V				18 (54.5)	7 (63.6)	3 (50.0)			
BMI (kg/m^2)	30.9 ± 5.6	33.0 ± 6.1	34.7 ± 6.4	38.2 ± 8.3**	42.7 ± 7.5**	36.6 ± 7.7	<0.001	0.43	0.03
BMI SDS (z score)	0.7 ± 0.7	0.9 ± 0.8	1.1 ± 0.8	3.8 ± 1.6**	4.6 ± 1.4**	3.3 ± 1.2	<0.001	0.21	0.20
HbA_{1c} (%)	5.6 ± 0.3	5.7 ± 0.4	7.9 ± 2.5	5.4 ± 0.8	5.6 ± 0.5	6.5 ± 1.2**	0.023	<0.001	0.067
HbA_{1c} (mmol/mol)	38 ± 4	38 ± 5	63 ± 27	36 ± 9	38 ± 5	47 ± 13	0.023	<0.001	0.067
Fasting insulin (pmol/mL)	115 ± 53	127 ± 78	206 ± 140	178 ± 86*	317 ± 200**	213 ± 26	<0.001	0.003	0.001
Fasting C-peptide (nmol/L)	0.71 ± 0.29	0.85 ± 0.45	0.94 ± 0.72	0.91 ± 0.51	1.67 ± 1.59	1.63 ± 0.59	<0.001	0.001	0.07
Fasting glucose (mmol/L)	5.1 ± 0.3	5.7 ± 0.7	8.3 ± 3.5	4.9 ± 0.4	5.3 ± 0.5	7.8 ± 1.7	0.27	<0.001	0.89
2-h glucose (mmol/L)	6.1 ± 1.1	7.8 ± 1.6	15.3 ± 4.4	6.6 ± 0.7	8.0 ± 1.0	7.8 ± 1.7	0.67	<0.001	0.85
Total cholesterol (mmol/L)	3.7 ± 0.7	3.7 ± 0.7	3.8 ± 0.6	3.3 ± 0.8*	3.0 ± 1.0*	2.7 ± 0.7**	<0.001	0.26	0.18
HDL (mmol/L)	0.9 ± 0.3	1.0 ± 0.3	0.8 ± 0.2	0.7 ± 0.2	0.7 ± 0.3**	0.7 ± 0.3	0.003	0.55	0.13
LDL (mmol/L)	2.4 ± 0.6	2.3 ± 0.7	2.4 ± 0.6	2.1 ± 0.6	1.8 ± 0.7	1.6 ± 0.4**	<0.001	0.09	0.28
Triglyceride (mmol/L)	1.0 ± 0.5	1.2 ± 0.5	1.8 ± 1.6	1.2 ± 0.6	1.8 ± 1.1**	1.6 ± 0.4	0.62	0.20	0.008
SBP (mmHg)	132 ± 17	139 ± 26	147 ± 25	114 ± 11**	133 ± 15	132 ± 8	0.14	0.002	0.045
SBP percentile				54 ± 30	86 ± 22	93 ± 7		<0.001	
DBP (mmHg)	79 ± 10	86 ± 20	87 ± 17	63 ± 6**	72 ± 9*	76 ± 7	<0.001	0.022	0.21
DBP percentile				43 ± 20	64 ± 25	78 ± 16		<0.001	

Data are presented as the mean ± SD, unless otherwise indicated. AA, African American; AW, American white; DBP, diastolic blood pressure; SBP, systolic blood pressure; SDS, SD score. *$P < 0.05$ compared with adults at the same stage; **$P < 0.01$ compared with adults at the same stage.

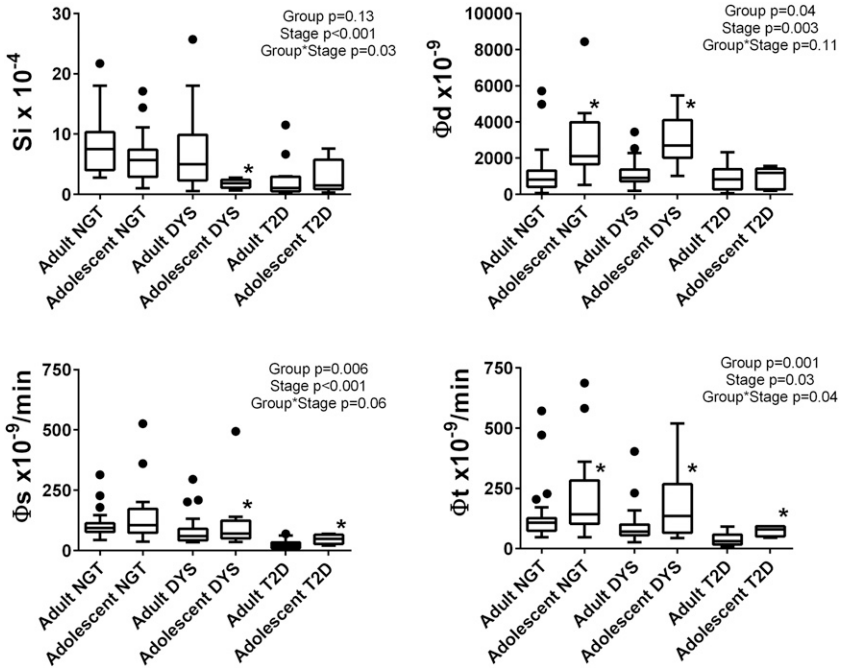

Figure 1—Comparisons between adults and adolescents in modeled parameters of insulin sensitivity and β-cell function across stages of glycemia. Top left panel: Insulin sensitivity (Si). Top right panel: Φd. Bottom left panel: Φs. Bottom right panel: Φt. DYS, dysglycemia; T2D, type 2 diabetes. Box plot presentation, with the bottom and top of the box presenting the 25th and 75th percentiles, respectively, and the middle line presenting the median. Whiskers present the 5th (bottom) and 95th (top) percentiles; filled circles outside of the whiskers represent individual data points that lie outside this distribution. Four such data points are above the scale for the Φs adolescent DYS group, as is one data point for the Φt adolescent T2D group. *Indicates statistical difference between adult and adolescent groups.

$P < 0.001$; DI-Φs NGT vs. dysglycemia $P = 0.027$; NGT vs. diabetes $P < 0.001$; dysglycemia vs. diabetes $P < 0.001$).

Among the obese adolescents studied, individuals with dysglycemia and diabetes had lower Si and higher HOMA-IR than NGT subjects (Table 2) (NGT vs. dysglycemia $P \leq 0.03$; NGT vs. diabetes $P \leq 0.002$) without a further difference between individuals with dysglycemia and those with diabetes. IGI and CPI were significantly worse in adolescents with type 2 diabetes than in individuals with dysglycemia or normoglycemia ($P \leq 0.001$). DIs derived from these direct measures of β-cell function differed stepwise across groups (DI-IGI NGT vs. dysglycemia $P = 0.076$; DI-CPI NGT vs. dysglycemia $P = 0.022$; all other comparisons between groups $P < 0.001$). In adolescents, Φt and Φs did not differ between any stages, but Φd mirrored IGI and CPI, with a marked reduction in individuals with diabetes compared with individuals with NGT or dysglycemia (Φd DM vs. NGT $P = 0.003$; Φd DM vs. dysglycemia $P = 0.007$). These relationships persisted after adjustment for insulin sensitivity (DI-Φd NGT vs. diabetes $P < 0.001$; dysglycemia vs. diabetes $P < 0.001$).

These differences are presented graphically for the modeled parameters in Fig. 1 and are presented in combinations as DIs in Fig. 2.

Differences Between Adolescents and Adults

Statistical tests of differences across clinical stages between adolescents and adults are presented in the rightmost columns of Table 2, with the key comparison found in the interaction of age × stage. Among insulin sensitivity measures, only HOMA-IR differed between age-groups as a whole ($P = 0.011$), whereas only Si demonstrated an interaction between age-group and glycemic stage ($P = 0.044$). This difference arose as a result of age-group differences in the progression of Si across glycemic stages. Although Si was equal between NGT adults and adolescents, it was lower in adolescents with dysglycemia than in adults with dysglycemia ($P = 0.025$). Because Si was lower in adults with diabetes than at other stages, Si was again equal between age-groups in type 2 diabetes. An analogous pattern was seen in HOMA-IR, which was greater ($P = 0.004$) in adolescents with dysglycemia owing to a higher HOMA-IR compared with NGT. Again, this difference was lost with diabetes, because adults with type 2 diabetes demonstrated a higher HOMA-IR than adults with dysglycemia. Summarizing these observations, significant worsening of IR characterizes youths with dysglycemia, whereas adults show a decrement instead at the later stage of overt type 2 diabetes.

The two direct measures of insulin secretion, IGI and CPI, both showed differences between age-groups as a whole (IGI $P = 0.003$; CPI $P = 0.018$), although after adjusting for insulin sensitivity a group difference was present only in DI-IGI ($P = 0.048$). Although small age-related differences in IGI and CPI existed at individual clinical stages of glycemia, these differences did not persist after correcting for insulin sensitivity. Neither the directly measured insulin secretion parameters nor their DIs showed age-dependent differences in changes across glycemic groups (Fig. 2).

The modeled indices of β-cell function Φt, Φs, and Φd showed differences between age-groups ($P < 0.001$ for all), which persisted after correcting for insulin sensitivity (DI-Φt $P < 0.001$, DI-Φs $P = 0.03$, DI-Φd $P = 0.004$). Φd was markedly higher in adolescents with NGT and dysglycemia compared with adults (NGT $P < 0.001$; dysglycemia $P = 0.005$), whereas the dramatically lower Φd in adolescents with type 2 diabetes did not differ from their adult counterparts. After adjusting for insulin sensitivity, NGT adolescents had a slightly higher DI-Φd ($P < 0.001$) than adults. Adults showed stepwise decreases in Φt, Φs, and their related DIs across glycemic stages. This pattern was not present in adolescents, demonstrating age-related variance in the differences between glycemic stages (P for age × stage: Φt $P = 0.015$; Φs $P = 0.012$; DI-Φt $P = 0.003$; DI-Φs $P = 0.01$) (Fig. 2).

CONCLUSIONS

Our findings demonstrate the relative dominance of IR requiring robust insulin secretion in the pathogenesis of adolescent dysglycemia, in contrast to progressive β-cell dysfunction driving adult dysglycemia. We found age-related differences in the nature of β-cell dysfunction across clinical stages of glycemia, with differences in the progression of Φs and Φd. To our knowledge, this is the first

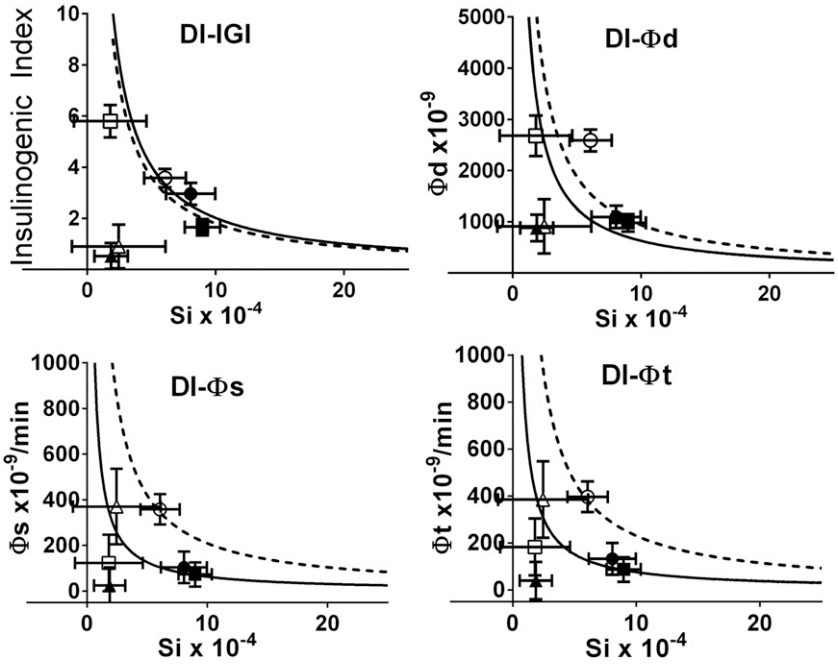

Figure 2—DI curves for normoglycemic adults and adolescents. Insulin sensitivity (Si) is plotted against different measures of insulin secretion: IGI, static insulin response (i.e., Φs), dynamic insulin response (i.e., Φd), and total insulin response (i.e., Φt). The mean DI curves for normoglycemic individuals are plotted; mean DI ± SD for adults and adolescents at each clinical stage are overlaid. Black circles, adult with normoglycemia; black squares, adult with dysglycemia; black triangles, adult with type 2 diabetes; dotted line, adolescent DI; solid line, adult DI; white circles, adolescent with normoglycemia; white squares, adolescent with dysglycemia; white triangles, adolescent with type 2 diabetes.

study directly comparing measures of insulin responsiveness and β-cell function between adolescents and adults.

This cohort of obese adolescents exhibited markedly higher insulin secretion than the adults, a widely recognized feature of puberty. With this, even obese adolescents with normoglycemia had a markedly higher Φd than overweight/obese adults (Figs. 1 and 2). This difference in β-cell function between groups was exaggerated in individuals with dysglycemia: where adults showed impaired Φs and Φt, adolescents continued to have robust insulin secretion but lower insulin sensitivity. Interestingly, these disparate combinations of dysfunction during dysglycemia (higher IR in adolescents and lower insulin secretion in adults) resulted in misleadingly comparable DIs. This is an instance where the DI can mask important between-group differences in the contributing components.

The trajectory implied by our cohort (IR driving the initial failure of glycemic tolerance in adolescents) is consistent with a longitudinal study that showed a marked decrease of Si in youths progressing from NGT to IGT compared with nonprogressors, in addition to a 20% reduction of insulin secretion in progressors (26). An adult longitudinal study (27) showed that Pima Indians progressing from NGT to diabetes had decrements in acute insulin secretory response from NGT to IGT and from IGT to diabetes, with stepwise reductions in insulin-stimulated glucose disposal. Of note, these and other studies show a combination of insulin secretory and sensitivity defects in the transition from NGT to IGT (7,8,10–12,23), but our comparison in overweight/obese individuals shows in particular a difference in Φd between adolescents and adults across the stages of dysglycemia. Prior longitudinal studies in adolescents have localized β-cell dysfunction to dynamic secretion in adolescents (26), whereas the dominance of dynamic or static secretory dysfunction in adults is less clear (7,9) and may depend on the type of glucose intolerance (9,28–30). Our observations suggest that adolescents and adults achieve dysglycemia differently—adolescents primarily via IR and adults primarily via β-cell dysfunction. Further work will be needed to understand how such differences in function arise, for example whether they are related principally to the physiology of puberty or perhaps reflect an underlying genetic risk that is brought out by puberty.

Our findings suggest that diabetes prevention should be approached differently in different age-groups. Adults with prediabetes may benefit more than adolescents from attempts to increase insulin production and secretion. Adolescents with obesity and prediabetes, in contrast, may benefit in particular from the optimization of insulin sensitivity because insulin secretion remains robust even during dysglycemia. Given the dramatic difference in dynamic secretion between adolescents with dysglycemia and type 2 diabetes, attempts to decrease β-cell demand could also focus on minimizing the stress upon this secretion component, for example by modulating short-term glucose loads.

Several weaknesses of these analyses should be acknowledged. The two cohorts we have compared were originally recruited for studies that were not designed to directly compare the two age-groups. One consequence of this is the difference in sample availability from early time points after glucose ingestion, and although our evaluations do not suggest that this adversely affected the ability to model the data, it remains possible that the between-group comparisons would differ if identical sampling had been available. Nevertheless, the opportunity to apply parallel methods to these groups provides valuable information that does not otherwise exist in the literature. As a consequence of the original inclusion criteria, youths with normoglycemia and dysglycemia had markedly higher BMI values than adults. Since obesity itself is a contributor to IR (31,32), these differences may have exaggerated modeled IR within the adolescent group. Nevertheless, the concurrent and markedly higher insulin secretion at these stages affirms that dysglycemia in adolescents arises from relative and not absolute insulin deficiency, driven primarily by IR. We calculated DIs using model-derived terms that have not been formally demonstrated to exhibit inverse hyperbolic relationships, but an inverse relationship is evident in our data even in the absence of formal testing. Our adult population had a higher proportion of African American patients, who are recognized to have a greater insulin response for a given degree of IR when compared with their Caucasian counterparts (33–36). However, if anything, this racial difference

Table 2—Indices of insulin sensitivity and β-cell function in adults and adolescents at each glycemic stage

	Adult NGT	Adult Dys	Adult T2D	Adol NGT	Adol Dys	Adol T2D	Group *P*	Stage *P*	Group* stage *P*
HOMA-IR (units)	2.8 [2.2–4.8] (24)	2.8 [2.3–5.9] (33)	8.4 [5.2–11.3] (17)*†	5.1 [3.6–6.4] (33)§	11.0 [4.8–14.2] (11)*§	10.8 [7.9–12.5] (6)*	0.53	<0.001	0.15
IGI (pmol/mmol)	206 [105–395] (24)	148 [93–294] (33)	38 [22–63] (17)*†	358 [182–555] (33)	684 [266–867] (11)§	79 [43–185] (6)*†	0.57	<0.001	0.07
CPI (nmol/mmol)	0.77 [0.43–1.18] (29)	0.61 [0.43–0.87] (35)	0.12 [0.07–0.19] (21)*†	0.97 [0.68–1.34] (30)	0.93 [0.62–1.57] (9)§	0.24 [0.01–0.56] (5)*†§	0.59	<0.001	0.20
$\Phi d \times 10^{-9}$	812 [380–1,267] (29)	899 [687–1,292] (36)	751 [254–1,288] (21)	1,905 [1,630–3,913] (31)§	2,703 [1,323–3,637] (10)§	1,189 [269–1,410] (5)*†	0.04	0.003	0.11
$\Phi s \times 10^{-9}$/min	93.4 [77.1–112.9] (29)	59.5 [42.1–89.7] (36)*	22.3 [9.9–33.0] (21)*†	105.0 [73.4–171.9] (31)	70.0 [50.5–124.3] (9)*§	51.4 [32.9–868.0] (5)§	0.006	<0.001	0.06
$\Phi t \times 10^{-9}$/min	106.4 [71.1–126.7] (29)	70.3 [55.6–100.3] (36)*	31.5 [17.5–58.2] (21)*†	143.1 [103.3–283.6] (31)§	135.8 [66.2–267.9] (9)§	92.9 [34.2–881.1] (5)§	0.001	0.025	0.043
Si (10^{-4} dL/kg/min per μU/mL)	7.5 [4.0–10.3] (22)	5.0 [2.3–9.9] (32)	0.7 [0.1–2.4] (16)*†	5.7 [2.9–7.4] (30)	1.8 [1.1–2.4] (10)*§	1.5 [0.2–4.8] (6)*	0.13	<0.001	0.034
DI-IGI (10^3 pmol/mmol × μU/mL per dL/kg/min)	966 [206–2,013] (22)	492 [248–1,873] (33)	321 [96–1,115] (16)*	1,585 [945–3,364] (33)§	3,508 [1,333–11,342] (11)*§	827 [538–1,703] (6)†	0.93	0.004	0.035
DI-CPI (pmol/mmol × μU/mL per dL/kg/min)	3.9 [1.4–7.3] (21)	2.2 [1.1–5.8] (33)	1.3 [0.5–2.1] (15)*	4.7 [2.8–7.9] (30)	7.7 [3.5–17.4] (9)§	2.4 [0.3–5.5] (5)†	0.72	0.01	0.17
DI-Φd (10^{-14} dL/kg/min per pmol/L)	3,344 [853–5,484] (23)	3,362 [1,297–5,451] (32)	241 [0–443] (15)*†	7,173 [3,640–11,861] (29)§	3,430 [1,475–6,303] (10)*	270 [101–3,445] (5)*†	0.001	<0.001	0.26
DI-Φs (10^{-14} dL/kg/min^2 per pmol/L)	546 [246–669] (22)	216 [97–522] (32)*	9 [0–26] (15)*†	369 [253–895] (28)	128 [42–181] (8)*§	70 [5–993] (5)§	0.02	<0.001	0.006
DI-Φt (10^{-14} dL/kg/min^2 per pmol/L)	533 [297–852] (21)	221 [109–593] (32)*	14 [0–30] (15)*†	650 [335–1,413] (28)	204 [78–181] (8)*§	94 [0–1,040] (5)§	0.001	<0.001	0.001

Main analyses used one-way ANCOVA incorporating adjustment for BMI *z* score. Analyses used log-transformed dependent variables. Data are presented as the median [interquartile range] (*n*) for the unadjusted data within each cell. Sample sizes vary according to the availability of data required for the calculation of each variable. Adol, adolescent; Dys, dysglycemia; T2D, type 2 diabetes. *$P < 0.05$ vs. NGT within age-group (significant for post hoc pairwise comparisons). †$P < 0.05$ dysglycemia vs. type 2 diabetes within age-group (significant for post hoc pairwise comparisons). §$P < 0.05$ compared with adults at same clinical stage (significant for post hoc pairwise comparisons).

would have blunted differences in insulin secretion between adults and adolescents and therefore does not detract from our finding of markedly higher secretion in adolescents. Among our adolescents, there was a much higher number of individuals at Tanner 3 stage within the normoglycemic category and none who had diabetes. This may reflect differences in susceptibility to pubertal stresses on glycemic control, but we did not have sufficient power to undertake these comparisons. Direct study of changes to β-cell function across Tanner stages would be valuable.

In summary, this study is the first to directly compare β-cell function and insulin responsivity in adults and adolescents. The present differences suggests that the two age-groups arrive at similar clinical stages via differing combinations of changes in IR and insulin secretion. The findings of this study reinforce current treatment and much research in prediabetes and diabetes in youths, which primarily emphasizes lifestyle modifications with or without the addition of insulin sensitizers (37–39). However, the trajectory of β-cell failure suggests that intervention before the development of type 2 diabetes may be especially instrumental within the adolescent age-group, to preserve relatively robust β-cell function, and provides a rationale for differential strategies in diabetes prevention.

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submitted. K.J.M. 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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