Published in final edited form as:

Pediatr Diabetes. 2013 March ; 14(2): 106–111. doi:10.1111/j.1399-5448.2012.00915.x.

Progressive deterioration of β -cell function in obese youth with type 2 diabetes

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Abstract

Objective—In adults, type 2 diabetes (T2DM) is characterized with progressive deterioration in insulin secretion. Data are scanty in youth. We investigated prospectively the change in β -cell function and in insulin sensitivity in youth with T2DM.

Research Design and Methods—Six adolescents with T2DM [hemoglobin A1c (HbA1c) $6.6 \pm 1.0\%$] underwent evaluation of hepatic glucose production (HGP; [6,6-²H₂] glucose), insulin-stimulated glucose disposal (Rd; hyperinsulinemic-euglycemic clamp), first- and second-phase insulin/C-peptide secretion (hyperglycemic clamp), body composition dual energy X-ray absorptiometry (DEXA), and abdominal adiposity (computed tomography) within 3 yr of the diagnosis of diabetes and after 12–16 months of follow-up.

Results—Weight, body mass index (37.1 ± 6.9), HbA1c ($6.3 \pm 0.7\%$), HGP (2.8 ± 1.2 mg/kg/min), and Rd (4.9 ± 3.4 mg/kg/min) did not change significantly from baseline. However, first-phase insulin and C-peptide declined (152.6 ± 261.2 vs. 75.9 ± 108.5 μ U/mL, $p=0.028$; 8.0 ± 6.3 vs. 5.9 ± 4.4 ng/mL, $p=0.048$, respectively) with no significant change in second-phase insulin/C-peptide. The rate of decline in β -cell function was $\sim 20\%$ per year.

Conclusions—After a median duration of 20 months of diabetes, youth with T2DM manifest a rapid decline in β -cell function with no significant changes in peripheral or hepatic insulin sensitivity. Interventions to retard this deterioration in β -cell function should be investigated.

Keywords

β -cell function; insulin secretion; youth type 2 diabetes

The pathophysiology of type 2 diabetes (T2DM) in youth involves impairments in insulin sensitivity and β -cell function, translating to around 86% lower insulin secretion relative to insulin sensitivity, compared with non-diabetic controls of similar body composition and abdominal adiposity (1, 2). Progressive deterioration of β -cell function is a well-recognized feature of the disease in adults (3, 4) and is a major challenge in maintaining glycemic control (3). Given the novelty of the disease and the paucity of patients in the pediatric age

group, there are limited longitudinal data regarding the natural history of T2DM in youth (5–7). These reports indicate rapid deterioration of β -cell function (6) during the course of treatment (7) compared to what is reported in adult large epidemiologic (3, 4) and cohort studies (8). In youth with recent onset T2DM, residual β -cell function is a significant determinant of glycemic control in small- (1) and large-scale studies such as the treatment options for type 2 diabetes in youth (TODAY) study (9). Glycemic control is an important factor to avert the comorbidities and complications of diabetes (10), which are identified in youth even at the time of diagnosis (11–13). However, data are sparse with respect to the rate of deterioration of β -cell function in youth with T2DM. Thus, we aimed to investigate prospectively the changes in insulin secretion and sensitivity in obese adolescents with T2DM. On the basis of our previous case reports (5, 6), we hypothesized that youth with T2DM will demonstrate accelerated deterioration in β -cell function compared with published data in adults.

Research design and methods

Study population

Six obese adolescents with T2DM (four females and two males; four African American and two American White) were studied prospectively within 3 yr of diagnosis of diabetes and after 12–16 months of follow-up. They were clinically diagnosed with T2DM (American Diabetes Association (ADA) consensus) and were persistently negative for glutamic acid decarboxylase (GAD) and insulinoma-associated protein-2 autoantibody with the DK harmonization assay (14) at baseline and at follow-up evaluations. They were on treatment with metformin (n=2), metformin and insulin (n=3), or insulin alone (n=1) at baseline, and either metformin alone (n=3) or metformin+insulin (n=3) at follow-up. Interval treatment was decided by the treating diabetologist. Metformin and long-acting insulin were discontinued 48 h before the clamp studies as before and glycemia maintained by administration of short-acting insulin as needed up to 6 h before the clamp studies (14, 15). Prior to enrollment, participants were required to have hemoglobin A1c (HbA1c) $\leq 8.0\%$ to avoid the potential confounding effect of chronic hyperglycemia on insulin sensitivity and secretion. All studies were approved by the Institutional Review Board of the University of Pittsburgh. Informed consent and assent were obtained. Clinical characteristics of the study subjects are summarized in Table 1.

Clamp studies

At baseline and at follow-up, participants were admitted twice within 4 wk to the Pediatric Clinical and Translational Research Center, once for a hyperinsulinemic-euglycemic clamp and the other time for a hyperglycemic clamp, in random order. One subject underwent a hyperglycemic clamp only at baseline and was not included in the comparison of insulin sensitivity.

In vivo insulin sensitivity—A fasting blood sample was obtained for determination of lipid profile and HbA1c. Fasting endogenous glucose production was measured with a primed constant-rate infusion of [6,6- $^2\text{H}_2$] glucose ($0.306 \pm 0.009 \mu\text{mol/kg/min}$) (Isotech, Miamisburg, OH, USA) as described previously (15). Insulin-stimulated glucose metabolism and insulin sensitivity were evaluated during a 3-h $80 \text{ mU/m}^2/\text{min}$ hyperinsulinemic-euglycemic clamp (15–17). Plasma glucose was clamped at 100 mg/dL with a variable rate infusion of 20% dextrose (15). Continuous indirect calorimetry by a ventilated hood (Deltatrac Metabolic Monitor, SensorMedics, Anaheim, CA, USA) was used to measure CO_2 production, O_2 consumption, and respiratory quotient. Measurements were made for 30 min at baseline and at the end of the euglycemic clamp (15).

In vivo insulin secretion—First- and second-phase insulin secretion and C-peptide were evaluated during a 2-h hyperglycemic clamp (225 mg/dL) as before (15).

Body composition

Body composition was determined by DEXA scan, and subcutaneous abdominal adipose tissue and visceral adipose tissue (VAT) by a single-slice computed tomography (CT) scan at L₄–L₅ (15). Body composition by DEXA was not possible for two individuals who exceeded the weight limit of the DEXA machine. One AA adolescent did not have VAT data at completion (technical error in CT acquisition).

Biochemical measurements

Plasma glucose was measured with a glucose analyzer (Yellow Springs Instrument Co., Yellow Springs, OH, USA), and insulin and C-peptide by radioimmunoassay as before (15–17). Two subjects (a boy and a girl) had very high insulin concentrations related to non-specific binding. Free insulin levels were determined for these two individuals. HbA_{1c} was measured by high-performance liquid chromatography (Tosoh Bioscience Inc., San Francisco, CA, USA) and lipids using the standards of the Centers for Disease Control and Prevention (15). Deuterium enrichment of glucose in the plasma was determined on a Hewlett-Packard Co. 5973 mass spectrometer (Palo Alto, CA, USA) coupled to a 6890 gas chromatograph (15). Pancreatic autoantibodies were determined using the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)-sponsored standardization assay in the Northwest Lipid Metabolism and Diabetes Research Laboratories, University of Washington (Seattle, WA, USA) as reported by us (14).

Calculations

Fasting hepatic glucose production (HGP) was calculated during the last 30 min of the 2-h isotope infusion according to steady-state tracer dilution equations (16). In the fasting state, hepatic insulin sensitivity was calculated as $1000/(\text{HGP} \times \text{fasting insulin})$ (16). Insulin-stimulated glucose disposal rate (R_d) was calculated during the last 30 min of the euglycemic clamp to be equal to the rate of exogenous glucose infusion (17). Insulin-stimulated carbohydrate oxidation rates were calculated according to the formulas of Frayn from the indirect calorimetry data (15). Non-oxidative glucose disposal was estimated by subtracting the rate of glucose oxidation from the total insulin-stimulated glucose disposal.

During the hyperglycemic clamp, the first- and second-phase insulin and C-peptide concentrations were calculated as described previously (15).

Statistics

Paired sample *t*-test or non-parametric Wilcoxon test were used to examine the difference of the means (or medians if non-parametric) at baseline and follow-up evaluations. Chi-squared test was used for comparison of categorical variables. Data are presented as mean $\pm$ SD. Two-tailed *p* 0.05 was considered statistically significant.

Results

Study subjects and fasting metabolic profile

All participants were in good glycemic control at baseline with a duration of diabetes less than 3 yr and after 12–16 months of follow-up (Table 1). Treatment modality was similar at baseline and follow-up except for one patient who initially was on insulin and at follow-up metformin had been added. Body mass index (BMI), percent body fat, and subcutaneous abdominal fat were not different at follow-up, but visceral fat was lower. Fasting glucose,

insulin, endogenous glucose production (HGP), hepatic insulin sensitivity, and lipid profile were not different between baseline and follow-up (Table 1).

Insulin-stimulated glucose disposal

During the hyperinsulinemic-euglycemic clamp, steady-state plasma glucose and insulin concentrations were not different between baseline and follow-up (101.1 ± 1.5 and 102.1 ± 1.6 mg/dL, and 292.8 ± 195.2 vs. 257.2 ± 113.4 μ U/mL). Insulin-stimulated total (4.3 ± 2.7 vs. 4.9 ± 3.4 mg/kg/min), oxidative (2.1 ± 0.8 vs. 2.0 ± 0.7 mg/kg/min), and non-oxidative (2.9 ± 1.6 vs. 2.9 ± 2.8 mg/kg/min) glucose disposal rates were not different at follow-up.

Insulin and C-peptide concentrations

During the hyperglycemic clamp, first-phase glucose concentration at baseline (225.0 ± 12.3 mg/dL) and follow-up (228.8 ± 8.0 mg/dL), and second-phase glucose concentration (228.5 ± 2.0 mg/dL) at baseline and follow-up (228.2 ± 2.3 mg/dL) were similar. First-phase insulin and C-peptide concentrations were significantly lower at follow-up with no significant difference in second-phase insulin and C-peptide concentrations (Fig. 1A, B). First-phase insulin concentration was 152.6 ± 261.2 μ U/mL at baseline and 75.9 ± 108.5 μ U/mL at follow-up, $p=0.028$; second-phase insulin concentration was 145.2 ± 167.7 μ U/mL at baseline and 149.2 ± 221.4 μ U/mL at follow-up. Similarly, first-phase C-peptide concentrations were lower at follow-up, 5.9 ± 4.4 ng/mL, compared to baseline, 8.0 ± 6.3 ng/mL, $p=0.048$, with no significant difference in second-phase C-peptide concentrations 8.7 ± 5.6 ng/mL at follow-up vs. 9.3 ± 3.9 ng/mL at baseline. Individual and treatment group changes in fasting and first-phase C-peptide levels are shown in Fig. 2A, B.

Rate of loss of β -cell function

The rate of change in β -cell function was calculated for each patient based on the change in individual insulin secretion divided by the duration between evaluations. The rate of deterioration of β -cell function was highly variable with a mean decrease of first-phase insulin of $28.4 \pm 16.2\%$ (mean $\pm$ SD) per year (range: 6–52%) and a mean decrease of first-phase C-peptide of $19.6 \pm 18.0\%$ per year (range: 0–49%). Eliminating one individual who had stable β -cell function over 1 yr does not change this data significantly with a $28.2 \pm 8.1\%$ decrease of first-phase insulin per year and a $23.7 \pm 7.5\%$ decrease of first-phase C-peptide per year.

Discussion

This prospective study of youth with T2DM, though limited in number, shows that there is a variable but relatively rapid deterioration of β -cell function over time, with no significant change in peripheral or hepatic insulin sensitivity in the absence of weight or BMI changes. Against the backdrop of the meager literature on the natural history of T2DM in youth, the current investigation advances our understanding of the progression of the pathophysiological aberrations in adolescents with T2DM albeit the limited number of participants. Our current data reveal ~20% decline in β -cell function per year in youth with T2DM. These results are consistent with the limited pediatric reports of rapid deterioration of insulin secretion or C-peptide levels in youth with T2DM (5–7) compared with adult studies (3, 4, 18). In a previous case report of an adolescent with T2DM followed over 6 yr, we found ~15% decline per year in β -cell function (6). Also, in a recent study, Katz et al. reported worsening of diabetes control and increasing insulin requirements by 1.5–2 yr after diagnosis of T2DM (7). Even though the latter study did not assess insulin sensitivity or secretion, it is highly likely that the inability to maintain glycemic control after the first 2 yr of diagnosis is a reflection of deteriorating β -cell function. These scarce pediatric data are in sharp contrast to adult studies reporting a lower rate of decline in β -cell function. In the

United Kingdom Prospective Diabetes Study (UKPDS), the estimated rate of decline of β -cell function, using the Homeostasis Model Assessment (HOMA %B) index, was about 7% per year (3, 4). The ADOPT (A Diabetes Outcome Progression Trial) study of drug naïve adults with T2DM with up to 3-yr duration utilized the insulinogenic index as a measure of β -cell function (18). The insulinogenic index declined in all three treatment groups after an initial improvement over the first 6 months of therapy with a rate of decrease of ~7–11% per year in the total cohort (18). A recent prospective study revealed stable fasting C-peptide levels in antibody-negative adults with diabetes over 20 yr of follow-up (8). In another prospective study with 12 yr of follow-up, insulin treatment was required in only one third of the adults who were consistently negative for GAD and ICA autoantibodies (19). Moreover, none of these individuals (n=57) had complete β -cell failure as they maintained fasting C-peptide levels over time (19). In this study, second-phase insulin and C-peptide levels were stable at follow-up. This may suggest that the deterioration in β -cell function may occur earlier for the first phase followed later with progressive deterioration in the second phase, but longer follow-up is needed to test this. Our findings also show significant inter-individual variability in β -cell function over time. Similarly, Katz et al. reported wide between-subject variability in C-peptide levels over the course of follow-up. This was partly related to whether or not these youth presented with ketoacidosis in which case they had overall lower C-peptide levels at presentation and follow-up (7). Also, in a cross-sectional evaluation of six adolescents with T2DM by Druet et al., the glucose- and arginine-stimulated insulin secretion rates were highly variable with no apparent relationship to the duration of diabetes (20). This variability may be related to different degrees of disease severity. This is consistent with the ADOPT findings of a decline in insulinogenic index of 5–10% in the cohort that completed the 4 yr of the study on study medication vs. ~16–20% rate of decline per year in the monotherapy failure group (18).

Another interesting observation of the current study is that in the absence of weight and BMI gain, peripheral insulin sensitivity did not deteriorate over time. This is consistent with the findings in adult longitudinal studies such as the UK Prospective Diabetes Study (4, 10). Our study is obviously hampered by the limited number of patients, reflecting the paucity of youth with T2DM and the difficulty of recruiting from this very challenging group of adolescents. Therefore, our study cannot address gender, racial, or ethnic differences. Participants had different duration of diabetes at the time of initial evaluation, partly because of the eligibility criterion of adequate glycemic control with HbA1c<8%. Another limitation is that interim medical therapy was determined clinically and not controlled in this observational prospective study. However, our rigorous methodology allowed us to identify important longitudinal changes in β -cell function in youth with T2DM on present-day standard medical therapy. The TODAY study, a large multicenter randomized controlled study of youth with T2DM, will contribute significantly to our knowledge in this area and verify our current observations (21).

In conclusion, our findings suggest that the course of β -cell deterioration in youth with T2DM is quite variable, with a rate of decline that seems to be more accelerated than what is reported in adults, but consistent with the accelerated rate of decline in adults with a more aggressive course of the disease (18). Therefore, in order to optimize the management of T2DM in youth, efforts should be geared toward β -cell preservation.

Acknowledgments

These studies would not have been possible without the nursing staff of the Pediatric Clinical and Translational Research Center at the Children's Hospital of Pittsburgh, the research team (Lori Bednarz, RN, CDE, and Nancy Guerra, CRNP); the laboratory expertise of Theresa Stauffer, MS, and Katie McDowell, BS, and most importantly the commitment of the study volunteers and their parents. This work was supported by United States Public Health Service grant K24 HD01357 (SA), Richard L. Day Endowed Chair (SA), Department of Defense (SA, FB, and

SJL), Thrasher Research Fund (FB and NG), the National Institutes of Health through Grant Numbers MO1 RR00084 (GCRC), UL1 RR024153, and UL1TR000005.

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Fig. 1.
(A) Insulin levels and (B) C-peptide levels at baseline (white circles) and at follow-up (dark circles) in youth with type 2 diabetes during the hyperglycemic clamp.

Fig. 2.

(A) Individual changes over time in fasting and first-phase C-peptide in adolescents with type 2 diabetes. (B) Changes over time in fasting and first-phase C-peptide combined for adolescents with similar therapies.

Table 1

Subject characteristics at baseline and at follow-up

	Baseline	Follow-up	p-value
Age (yr)	14.4 ± 1.9	15.6 ± 1.9	<0.001
Duration of type 2 diabetes (months) (range)	13.3 ± 14.7 (1.5–34)	26.7 ± 14.7 (14.5–46)	<0.001
Body mass index (kg/m ²)	37.1 ± 7.6	37.1 ± 6.9	0.9
% Body fat (%) (n=4)	42.3 ± 7.6	42.2 ± 9.3	0.9
Subcutaneous abdominal fat (cm ²) (n=5)	546.6 ± 160.5	534.5 ± 180.2	0.4
Visceral fat (cm ²) (n=5)	96.7 ± 82.0	87.8 ± 79.7	0.022
Hemoglobin A1c (%)	6.6 ± 1.0	6.3 ± 0.7	0.6
Treatment:			
Insulin alone	1	0	0.5
Metformin	3	3	
Insulin + Metformin	2	3	
Fasting glucose (mg/dL)	120.3 ± 26.9	130.0 ± 41.7	0.5
Fasting insulin (μU/mL)	42.7 ± 32.5	41.4 ± 34.2	0.7
Hepatic glucose production (mg/kg/min)	2.9 ± 1.0	2.8 ± 1.2	0.7
Hepatic insulin sensitivity (mg/kg/min per μU/mL) ⁻¹	12.5 ± 11.4	13.3 ± 9.6	0.8
Rate of glucose disposal (Rd) (mg/kg/min)	4.3 ± 2.7	4.9 ± 3.4	0.4
Cholesterol (mg/dL)	156.0 ± 37.9	151.2 ± 24.5	0.6
Low-density lipoprotein cholesterol (mg/dL)	99.4 ± 30.1	89.7 ± 26.2	0.3
High-density lipoprotein cholesterol (mg/dL)	36.0 ± 5.5	30.2 ± 1.9	0.1
Triglycerides (mg/dL)	103.6 ± 27.9	156.4 ± 54.1	0.2