The Presence of GAD and IA-2 Antibodies in Youth With a Type 2 Diabetes Phenotype

Results from the TODAY study

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OBJECTIVE — To determine the frequency of islet cell autoimmunity in youth clinically diagnosed with type 2 diabetes and describe associated clinical and laboratory findings.

RESEARCH DESIGN AND METHODS — Children (10–17 years) diagnosed with type 2 diabetes were screened for participation in the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study. Measurements included GAD-65 and insulinoma-associated protein 2 autoantibodies using the new National Institute of Diabetes and Digestive and Kidney Diseases/National Institutes of Health (NIDDK/NIH) standardized assays, a physical examination, and fasting lipid, C-peptide, and A1C determinations.

RESULTS — Of the 1,206 subjects screened and considered clinically to have type 2 diabetes, 118 (9.8%) were antibody positive; of these, 71 (5.9%) were positive for a single antibody, and 47 were positive (3.9%) for both antibodies. Diabetes autoantibody (DAA) positivity was significantly associated with race ($P < 0.0001$), with positive subjects more likely to be white (40.7 vs. 19%) ($P < 0.0001$) and male (51.7 vs. 35.7%) ($P = 0.0007$). BMI, BMI *z* score, C-peptide, A1C, triglycerides, HDL cholesterol, and blood pressure were significantly different by antibody status. The antibody-positive subjects were less likely to display characteristics clinically associated with type 2 diabetes and a metabolic syndrome phenotype, although the range for BMI *z* score, blood pressure, fasting C-peptide, and serum lipids overlapped between antibody-positive and antibody-negative subjects.

CONCLUSIONS — Obese youth with a clinical diagnosis of type 2 diabetes may have evidence of islet autoimmunity contributing to insulin deficiency. As a group, patients with DAA have clinical characteristics significantly different from those without DAA. However, without islet autoantibody analysis, these characteristics cannot reliably distinguish between obese young individuals with type 2 diabetes and those with autoimmune diabetes.

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Type 2 diabetes in youth was rarely reported before the 1990s, but increased in the late 1990s, associated with the burgeoning of childhood obesity (1–3). Type 2 diabetes now accounts for 15–87% of new-onset diabetes in U.S. youth aged 10–20 years, varying with race/ethnicity (4). In addition, there have been significant increases in the occurrence of type 1 diabetes in the last 25 years (5–7). Given the obesity epidemic, many youth with type 1 diabetes are either overweight or obese at diagnosis (8,9), making it difficult for clinicians to distinguish between type 1 and type 2 diabetes based on weight alone. As the classic criteria for distinguishing between these two major types of diabetes (i.e., age at onset and weight) are increasingly blurred, there has been a need to develop better methods of diabetes classification in youth.

This dilemma was highlighted by the SEARCH for Diabetes in Youth study, which reported that 21.2% of children aged 10–19 years of age with physician-identified type 2 diabetes were found to be positive for GAD-65 antibodies (4). Although the significance of these antibodies in children with phenotypic type 2 diabetes is not currently understood, in adults in the UK Prospective Diabetes Study (UKPDS) who had positive GAD-65 antibodies and physician-diagnosed type 2 diabetes, oral treatment failed significantly more rapidly than in those without autoimmunity (94 vs. 14% at 6 years) (10). These and other studies suggest that there are clinically significant differences between individuals with clinical signs of type 2 diabetes and islet autoimmunity compared with those without evidence of autoimmunity.

With the dramatic increase in type 2 diabetes in youth of all ethnic origins, the importance of determining the effectiveness of treatment options became a child health priority. The Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study is a National Institutes of Health (NIH)-sponsored multicenter clinical trial designed to compare

treatment with metformin alone, metformin with rosiglitazone, and metformin with an intensive lifestyle intervention program in children 10–17 years of age (11). In designing the TODAY study, the UKPDS experience led to a decision to exclude islet antibody-positive individuals from the trial. This report examines islet autoimmunity in youth who were considered by pediatric endocrinologists to have type 2 diabetes based on their phenotypic presentation. Subjects were assessed for islet autoimmunity at the screening visit for the TODAY study; those with islet autoimmunity were excluded from participation. Clinical and laboratory differences between islet antibody-positive and antibody-negative participants at screening are described.

RESEARCH DESIGN AND METHODS

The TODAY Study Group is composed of 15 clinical centers, a coordinating center, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) project office, and central cores and laboratories (a list of the TODAY study centers and contributing investigators at each center and of industries supporting the TODAY trial is found in an online appendix, available at http://care.diabetesjournals.org/cgi/content/full/dc10-0373/DC1). The protocol was approved by an External Evaluation Committee convened by NIDDK and by the institutional review board of each participating center. A Data and Safety Monitoring Board convened by NIDDK reviews progress and safety regularly throughout the study. The TODAY study rationale, design, and methods have been described previously (11). All participants provided informed consent, and minor children confirmed assent according to local guidelines before participation in the screening visit.

Screening visits (n = 1,211) were conducted from May 2004 to September 2008. The current article reports the results of the 1,206 subjects who had autoantibody determinations. Only patients with fasting C-peptide levels >0.6 ng/ml and negative IA-2 and GAD-65 autoantibodies were eligible for participation in the TODAY study.

Eligibility criteria included age 10–17 years, diagnosis of diabetes consistent with type 2 diabetes by standard criteria (12) with duration <2 years, and BMI ≥85th percentile at the visit or at diagnosis. Exclusion criteria included diabetic ketoacidosis at any time after diagnosis, except for a single episode related to a significant intercurrent medical illness. Eligible subjects were screened while using their current diabetes treatment, and rapid-acting insulin was held until after the assessment. The assessment included height, weight, calculation of BMI, and presence of acanthosis nigricans by inspection. Blood pressure was measured using an automated device (CAS Medical Systems) and appropriately sized cuff and checked three times after the participant rested in the seated position for 5 min. Race/ethnicity was determined by self-report using the 2000 Census collection format. A family history of diabetes and additional demographic data were obtained. Laboratory studies were performed in the fasted state and included a lipid profile (total, LDL, and HDL cholesterol and triglycerides), C-peptide, insulinoma-associated protein 2 (IA-2) and GAD-65 autoantibodies, and A1C.

Laboratory methods

Samples were processed following standardized procedures and shipped on dry ice to the Northwest Lipid Metabolism and Diabetes Research Laboratories, University of Washington (Seattle, WA). C-peptide was measured by a two-site immunoenzymatic assay on a dedicated instrument (Tosoh Bioscience, San Francisco, CA). The assay sensitivity is 0.05 ng/ml. A1C levels were determined by an automated nonporous ion-exchange high-performance liquid chromatography system (G7; Tosoh Bioscience). Measurements of total cholesterol, triglycerides, and HDL cholesterol were performed enzymatically using a Roche reagent on a Roche Pmodule autoanalyzer. LDL cholesterol levels were calculated by the Friedewald equation for samples with triglycerides <400 mg/dl and by the Lipid Research Clinic Beta Quantification approach for those with triglycerides ≥400 mg/dl.

Islet cell autoantibody assays for IA-2 and GAD-65 were initially performed at the TODAY central laboratory. They were subsequently confirmed at the Diabetes Research Institute Munich Laboratory (Munich, Germany) using the new, NIDDK standardized assay with standardized ^{35}S-labeled GAD-65 or IA2-IC proteins, according to the harmonized NIDDK/NIH autoantibody methods. The assays were calibrated using a set of standards with predetermined levels of GAD-65 or IA-2 antibodies expressed in arbitrary NIDDK units (DK units per ml). The GAD-65 assay is 76% sensitive and 97% specific, and the IA-2 assay is 64% sensitive and 99% specific. In the Diabetes Research Institute Munich Laboratory, a GAD-65–positive value is ≥43 DK units/ml; an IA-2–positive value is ≥5 DK units/ml.

Statistical methods

Data reported in this article primarily include descriptive statistics of the participants at the time of screening. When appropriate, data are reported as median with percentiles, mean ± SD, or percentage within a category. Comparisons by antibody status were made by ANOVA in the case of normally distributed continuous variables, the Kruskal-Wallis test for nonnormally distributed continuous variables, and the χ^2 test for categorical variables. No adjustment was made for multiple comparisons.

RESULTS

Participants (n = 1,206) had a median time from diabetes diagnosis to screening of 2.0 months (25th percentile <1, 75th percentile 6.3) and a median age of 14.0 (12,13) years. More than half were female (62.8%) and the majority were from racial and ethnic minority groups (21.1% white, 34.0% Hispanic, 35.2% black, and 5.3% American Indian). GAD-65 and IA-2 antibody titers are shown in Fig. 1; 118 (9.8%) were antibody positive, with 71 (5.9%) of these positive for a single antibody and 47 (3.9%) positive for both GAD-65 and IA-2 antibodies. Of the 71 with a single antibody, 29 were positive for only GAD-65 and 42 were positive for only IA-2 (Fig. 1*A* and *B*).

Demographic characteristics are shown in Table 1 according to diabetes autoantibody (DAA) status. Distributions of race/ethnicity and sex were significantly different ($P < 0.0001$ and $P = 0.0007$, respectively). The antibody-positive participants were more likely to be white (40.7%) and male (51.7%) than the antibody-negative subjects (19% white; 35.7% male). Those with positive DAA status were less likely to have a family history of diabetes in a first-degree relative than the antibody-negative participants (31.4 and 53.2%, respectively; $P < 0.0001$). Almost 1 in 5 (18.8%) of the white subjects were antibody positive compared with less than 1 in 10 of the screened black (6.8%), Hispanic (8%), or American Indian subjects (7.8%).

The clinical and laboratory findings

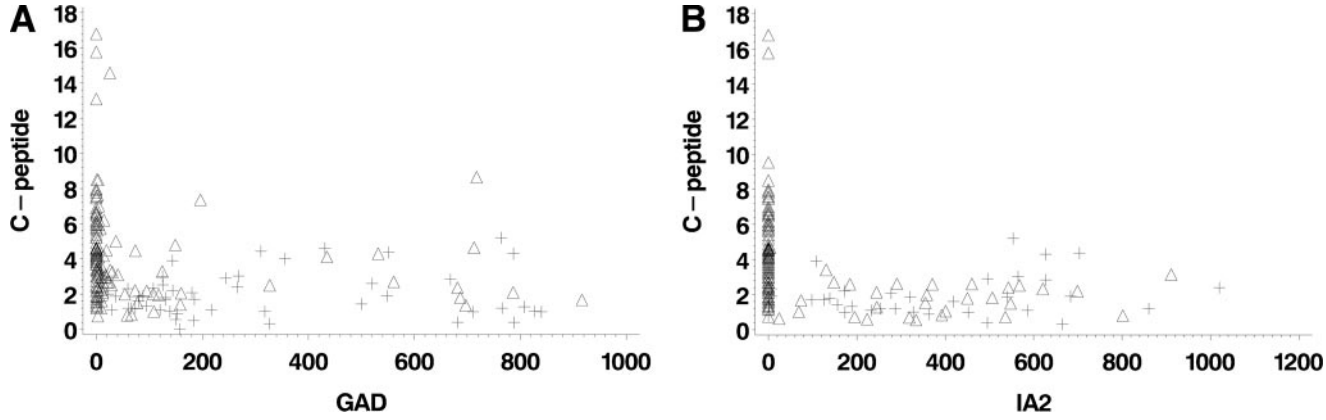

Figure 1—*Fasting C-peptide vs. antibody titer. Antibody levels are represented in NIDDK/NIH standardized DK units, and C-peptide values are measured as nanograms per milliliter.* A*: GAD-65 antibody titers vs. fasting C-peptide. △, GAD-65 values for IA-2–negative subjects; +, GAD-65 values for IA-2–positive subjects. GAD-65 values ≥45 DK units/ml are positive.* B*: IA-2 antibody titers vs. fasting C-peptide. △, IA-2 values for GAD-65–negative subjects; +, IA-2 values for GAD-65–positive subjects. IA-2 values ≥5.0 DK units/ml are positive. The normal range for fasting C-peptide is 0.5–3.0 ng/ml.*

of subjects are shown in Table 2 by antibody status. Both antibody-negative and -positive groups were overweight or obese, as required for screening eligibility; however, the median BMI and BMI *z* score were significantly lower in the DAA-positive group ($P < 0.0001$). Overall, the antibody-positive subjects were less likely to display clinical characteristics usually associated with type 2 diabetes and the metabolic syndrome phenotype, including elevations in blood pressure and triglycerides, low HDL cholesterol, and the presence of acanthosis nigricans. Insulin use was significantly greater in the DAA-positive group than in the DAA-negative group (54.2 vs. 38.8%, respectively; $P = 0.0013$). Similarly, the DAA-positive group had a lower median C-peptide level than the DAA-negative group (2.0 compared with 3.8 ng/ml, respectively; $P < 0.0001$). Importantly, the antibody-negative participants had 7.31 (95% CI 4.62–11.57) times the odds of having a fasting C-peptide value above the upper limit of normal (>3 ng/ml) compared with antibody-positive participants; when adjusted for BMI *z* score, the odds ratio remains significant at 5.11 (95% CI 3.13–8.34). All differences between antibody-positive and -negative subjects remained significant when analyzed by number of positive antibodies.

Figure 2 shows the distributions of BMI *z* scores and C-peptide levels according to antibody status. Figure 2*A* demonstrates that there is almost complete overlap of BMI *z* scores among the antibody-negative, single antibody–positive, and double antibody–positive participants, although mean and median BMI *z* scores were significantly lower in the DAA-positive groups. Although the C-peptide values of the DAA-positive groups are included within the range of the values for the DAA-negative group, the distributions of C-peptide levels are significantly different for DAA-positive and -negative subjects, with many of the DAA-negative subjects having C-peptide values greater than the highest values found in the DAA-positive groups.

Table 1—*Demographic findings in antibody-negative and antibody-positive groups*

	n	Antibody-negative	*n*	Antibody-positive	*P* value
n		1,088		118	
Age (years)	1,088	14 (12, 15)	118	13 (12, 15)	NS
Duration of diabetes (months)	1,045	1.9 (0.7, 6.1)	113	2.5 (0.7, 7.3)	NS
Race/ethnicity (%)	1,088		118		
White		19.0		40.7	
Black		36.3		24.6	
Hispanic		34.7		28.0	
Asian		2.2		0.8	
American Indian		5.4		4.2	
Other		2.3		1.7	
Female sex (%)	1,088	64.3	118	48.3	0.0007
Parent or full sibling has diabetes (%)	875	53.2	93	31.4	<0.0001

Data are % or median (25th, 75th percentile). NS, not significant.

CONCLUSIONS — Using the new NIH standardized assay, 9.8% (118 of 1,206) of youth with BMI ≥85th percentile and thought by pediatric endocrinologists to have type 2 diabetes were positive for GAD-65 and/or IA-2 antibodies. Additional antibody-positive individuals may have been identified had insulin autoantibodies or zinc transporter 8 autoantibodies been measured. Previous insulin use or unclear history of insulin use in the majority of subjects prevented the determination of insulin autoantibodies, and zinc transporter 8 antibody analysis was not available at the outset of the TODAY study (14).

The antibody-positive group is significantly different from the antibody-negative group, with fewer clinical and laboratory findings characteristic of type 2 diabetes and more findings similar to those found in type 1 diabetes, i.e., a more equal male-to-female ratio, more likely to be white, higher HDL cholesterol, and lower triglycerides, C-peptide, and BMI *z* scores (even though participation was limited to overweight or obese individu-

Table 2—*Physical, clinical, and fasting laboratory findings by diabetes antibody status at the screening assessment*

	n	Antibody-negative	*n*	Antibody-positive	*P* value
n		1,088		118	
BMI	1,082	34.9 (30.3, 39.9)	115	29.1 (25.4, 35.2)	<0.0001
BMI *z* score	1,082	2.3 (2.1, 2.6)	115	1.9 (1.5, 2.4)	<0.0001
Systolic blood pressure	1,075	115.0 (107.7, 123.3)	114	110.5 (103.7, 115.7)	<0.0001
Diastolic blood pressure	1,075	68.3 (63.3, 74.3)	114	64.7 (60.3, 70.0)	<0.0001
Acanthosis nigricans (%)	1,032	84.4	108	67.8	<0.0001
Insulin use (%)	1,088	38.8	118	54.2	0.0013
Metformin use (%)	1,088	73.8	117	62.7	0.0155
A1C (normal = 3.9–6.1%)	1,082	6.9 (6.0, 8.8)	117	7.6 (6.2, 10.1)	0.0111
Fasting C-peptide (normal = 0.5–3.0 ng/ml)	1,088	3.8 (2.6, 5.2)	118	2.0 (1.2, 2.7)	<0.0001
Total cholesterol	1,086	156 (135, 179)	118	151 (133, 173)	0.1156
LDL cholesterol	1,085	92 (74, 111)	117	87 (74, 101)	0.1351
HDL cholesterol	1,085	39 (33, 46)	117	43 (37, 51)	<0.0001
Triglycerides	1,086	106.5 (73, 156)	118	77 (56, 120)	<0.0001

Data are % or median (25th, 75th percentile).

als). However, one cannot reliably distinguish phenotypically between individual participants with positive GAD-65 or IA-2 antibodies and those without antibodies. Although the median BMI and C-peptide values are significantly different between these two groups, the ranges of both BMI *z* scores and C-peptide levels in the antibody-positive subjects fall within the range of those of the antibody-negative individuals. Similar results apply to lipid and blood pressure levels.

The finding of islet cell antibody-positive adolescent patients in participants screened in the TODAY study is consistent with other reports (13,15). In SEARCH, 21.2% of children 10–19 years of age with physician-identified type 2 diabetes were found to be positive for GAD-65 antibodies (4). The higher rate of diabetes autoimmunity identified in youth with "type 2 diabetes" in SEARCH may be due to a higher background non-Hispanic white population. In addition, in the SEARCH report, the method used for determining DAA was not the NIDDK standardized assay, which makes it difficult to directly compare the results. Recently, all SEARCH samples were reanalyzed with the standardized assay; when these data are published, it will be interesting to compare our results to the SEARCH data.

Whether these autoantibody-positive individuals have both autoimmune type 1 diabetes and insulin-resistant type 2 diabetes or more typical type 1 diabetes presenting in overweight or have insulin resistance due to their obesity is unclear and controversial (16,17). The GAD-65 antibody–positive type 2 diabetes group in SEARCH had a mean fasting C-peptide level of 2.83 ± 1.8 ng/ml (measured in the same laboratory used in the TODAY study), which is modestly higher than the mean found in our subjects (2.30 ± 1.62 ng/ml) but lower than that of the antibody-negative participants in both the TODAY study (4.13 ± 2.22 ng/ml) and SEARCH (3.71 ± 2.2 ng/ml). However, the C-peptide in screened TODAY subjects reported here was substantially higher than that found in individuals with physician-diagnosed type 1 diabetes in SEARCH (fasting C-peptide 0.75 ± 0.6 ng/ml), suggesting more insulin resistance in obese youth with a type 2 diabetes phenotype with less insulin deficiency compared with a more typical normal-weight adolescent with type 1 diabetes.

A recent report compared insulin resistance in youth with clinically diagnosed type 2 diabetes and positive DAA, youth with type 2 diabetes and negative DAA, and obese youth with normal glucose tolerance (17). These authors reported that insulin sensitivity was significantly impaired in DAA-negative type 2 diabetic youth compared with youth with islet autoimmunity and obese control youth. However, there was no difference in insulin sensitivity between the latter two groups, suggesting that the degree of insulin resistance in DAA-positive youth is more typical of obesity than that of type 2 diabetic youth, in whom an inherent genetic/epigenetic factor is believed to play a role. Because the youth with autoimmunity do not have the same degree of insulin resistance as that found in those with DAA-negative type 2 diabetes, the progression to diabetes must arise in part from a greater component of β-cell failure compared with that in the DAA-negative type 2 diabetic youth, possibly as a result of islet autoimmunity. Indeed, these authors demonstrated that insulin secretion during a hyperglycemic clamp was significantly lower in phenotypic type 2 diabetic youth with positive DAA than in youth with negative DAA (17).

The biochemical profile of our antibody-positive group is consistent with these findings and those reported in adult subjects enrolled in A Diabetes Outcome Progression Trial (ADOPT), a treatment trial in physician-diagnosed type 2 diabetes. In this trial, subjects with positive GAD-65 antibodies had lower fasting insulin, significantly lower homeostasis model assessment of insulin resistance and triglycerides and higher HDL cholesterol than in those without GAD-65 autoantibodies, suggesting less insulin resistance in the DAA-positive subjects (18). The GAD-65–positive and –negative groups did not differ overall with respect to age, sex, BMI, waist circumference, fasting glucose, or A1C levels. These results indicate that adolescent and adult patients with "antibody-positive type 2 diabetes" have a similar clinical and metabolic phenotype, suggesting a similar etiopathology. Thus, taken together with our data, these results indicate that obese individuals with diabetes and autoimmunity are closer physiologically to their normal-weight peers with type 1 diabetes than to antibody-negative individuals with type 2 diabetes.

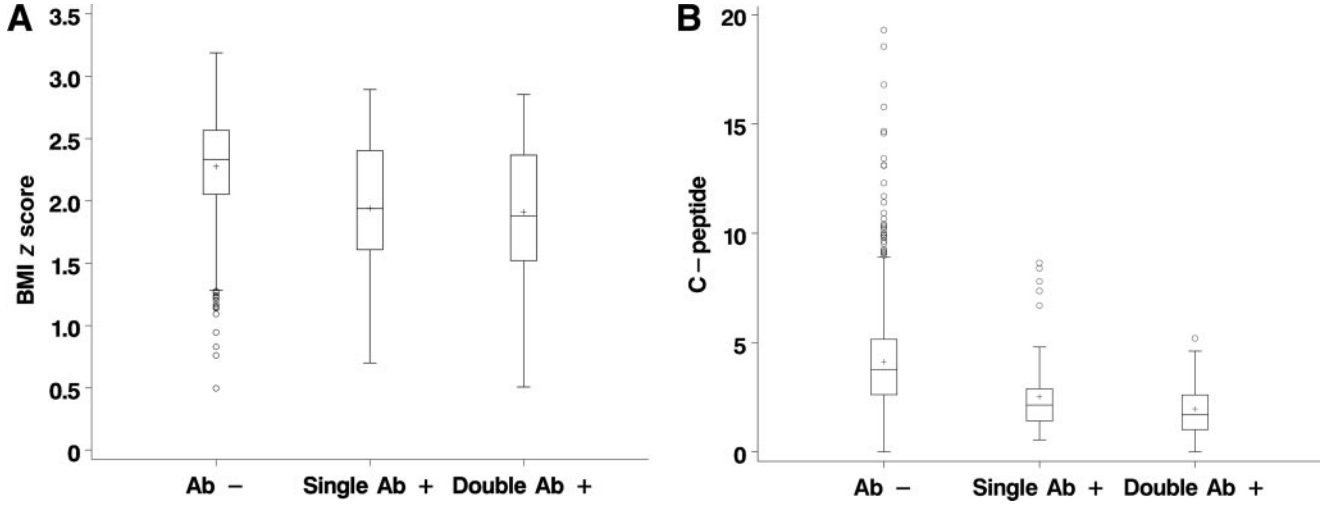

Figure 2—*Box-and-whisker plots of BMI z score* (A) *and fasting C-peptide* (B) *by antibody (Ab) status. + identifies the mean, and the line through the middle of the box is the median. The upper and lower edges of the box are the 75th and 25th percentiles, respectively. The upper whisker is drawn between the 75th percentile (upper edge of the box) and the largest observed value <1.5 times the interquartile range, above the 75th percentile. The lower whisker is drawn between the 25th percentile and the smallest observed value >1.5 times the interquartile range below the 25th percentile. ○, outliers.*

There are few reports of treatment outcomes in type 2 diabetic individuals who are DAA-positive. The UKPDS trial reported that in young GAD-positive subjects with physician-diagnosed type 2 diabetes oral treatment failed more rapidly than in those without autoimmunity; 94% required insulin by the end of the study, compared with 14% of antibody-negative subjects. The mean time to insulin requirement was <3 years in the antibody-positive group (10). A smaller report of adolescents initially diagnosed with type 2 diabetes but later determined to have markers predictive of risk for type 1 diabetes indicated that these youth required insulin therapy within 4 years (19).

Our results, combined with the above data, emphasize the importance of determining islet autoantibodies in all youth and young adults thought to have type 2 diabetes. Young people with clinically diagnosed type 2 diabetes and unrecognized islet autoimmunity may develop metabolic decompensation with rapid onset of a requirement for insulin. Knowledge of the presence of autoimmunity in overweight and obese young people with diabetes can direct decisions regarding initiation of insulin therapy to avoid this preventable morbidity. In addition, all young people with type 2 diabetes should be instructed about the signs and symptoms of severe insulin deficiency and the importance of seeking prompt medical attention. Finally, obese youth with diabetes being considered for inclusion in treatment trials and studies evaluating outcomes of type 2 diabetes should have determination of islet autoimmunity, as the clinical course and outcomes for those with DAA may be significantly different.

The strengths of this study were the large sample size, the racial/ethnic diversity, and the use of the new NIDDK/NIH standardized islet cell antibody assay. This study was limited to those with a diagnosis of obesity-associated type 2 diabetes (BMI ≥85th percentile for age and sex), so our findings may not generalize to all youth diagnosed clinically with type 2 diabetes.

Future studies of antibody-positive adolescents and young adults with clinical features of type 2 diabetes are needed to determine their clinical course and optimal treatment regimens. It will be important to determine whether early insulin therapy or other treatment approaches will be effective in preserving residual β-cell function in these youth.

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No potential conflicts of interest relevant to this article were reported.

G.J.K. designed the study and collected and analyzed data, wrote the manuscript, and reviewed/edited the manuscript. L.P. designed the study, performed statistical analysis, wrote the manuscript, and reviewed/edited the manuscript. S.A. and L.L. designed the study, collected and analyzed data, wrote the manuscript, and reviewed/edited the manuscript. K.C.C., F.K., and R.S.W. designed the study, collected and analyzed data, and reviewed/edited the manuscript. L.C. designed the study and collected and analyzed data. S.M. supervised the laboratory for specimen analysis, wrote the manuscript, and reviewed/edited the manuscript. S.E.T. designed the study, collected and analyzed data, research data, wrote the manuscript, and reviewed/edited the manuscript. B.L. designed the study, analyzed data, wrote the manuscript, and reviewed/edited the manuscript.

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