Testing the Accelerator Hypothesis

Body size, β-cell function, and age at onset of type 1 (autoimmune) diabetes

DANA DABELEA, MD, PHD[1]
RALPH B. D'AGOSTINO, JR., PHD[2]
ELIZABETH J. MAYER-DAVIS, PHD[3]
DAVID J. PETTITT, MD[4]
GIUSEPPINA IMPERATORE, MD, PHD[5]
LARRY M. DOLAN, MD[6]
CATHERINE PIHOKER, MD[7]
TERESA A. HILLIER, MD[8]
SANTICA M. MARCOVINA, PHD[9]
BARBARA LINDER, MD[10]
ANDREA M. RUGGIERO, MD, PHD[2]
RICHARD F. HAMMAN, MD, DRPH[1]
FOR THE SEARCH FOR DIABETES IN YOUTH STUDY GROUP

OBJECTIVE — The "accelerator hypothesis" predicts that fatness is associated with an earlier age at onset of type 1 diabetes. We tested the hypothesis using data from the SEARCH for Diabetes in Youth study.

RESEARCH DESIGN AND METHODS — Subjects were 449 youth aged <20 years at diagnosis who had positive results for diabetes antibodies measured 3–12 months after diagnosis (mean 7.6 months). The relationships between age at diagnosis and fatness were examined using BMI as measured at the SEARCH visit and reported birth weight, both expressed as SD scores (SDSs).

RESULTS — Univariately, BMI SDS was not related to age at diagnosis. In multiple linear regression, adjusted for potential confounders, a significant interaction was found between BMI SDS and fasting C-peptide (FCP) on onset age ($P < 0.0001$). This interaction remained unchanged after additionally controlling for number and titers of diabetes antibodies. An inverse association between BMI and age at diagnosis was present only among subjects with FCP levels below the median (<0.5 ng/ml) (regression coefficient −7.9, $P = 0.003$). A decrease of 1 SDS in birth weight (639 g) was also associated with an ~5-month earlier age at diagnosis ($P = 0.008$), independent of sex, race/ethnicity, current BMI, FCP, and number of diabetes antibodies.

CONCLUSIONS — Increasing BMI is associated with younger age at diagnosis of type 1 diabetes only among those U.S. youth with reduced β-cell function. The intrauterine environment may also be an important determinant of age at onset of type 1 diabetes.

Diabetes Care **29:290–294, 2006**

The "accelerator hypothesis" postulates that obesity-associated insulin resistance accelerates the disease process of type 1 diabetes. The marker is an earlier age at onset of type 1 diabetes associated with increased BMI (1).

In contemporary societies, increasing childhood obesity may account for the increasing incidence and younger age at onset of type 1 diabetes (2) and for the difficulty in distinguishing between type 1 and type 2 diabetes (3,4). The accelerator hypothesis suggests that the increased incidence of type 1 diabetes may be caused by an accelerated progression rather than by an increase in the absolute lifetime risk (1). In support of accelerated progression, the incidence of type 1 diabetes rose in children (0–14 years) but fell later in life (15–34 or 39 years) in Sweden (5,6) and Belgium (7).

Obesity-induced insulin resistance may upregulate the β-cells, which become susceptible to an autoimmune attack (8). If this is correct, we can hypothesize that the association between BMI and onset age, if present, may be mediated through an intensified autoimmune response.

Studies have linked in utero growth restriction with an increased risk for future chronic diseases, including obesity and insulin resistance. The association between birth weight and age at onset of type 1 diabetes has not been systematically studied.

We aimed to test aspects of the accelerator hypothesis using data from the SEARCH for Diabetes in Youth (9). We hypothesized that higher BMI in the 1st year after diagnosis and lower birth weight would be associated independently with earlier age at diagnosis of type 1 diabetes. BMI measured in youth with type 1 diabetes 6 months after onset correlates well with prediagnosis measurements ($r = 0.64$, $P < 0.0001$) (10). We also hypothesized that these associations, if present, would be mediated through an intensified autoimmune response, as reflected by higher number or titers of diabetes antibodies (11).

RESEARCH DESIGN AND METHODS

— SEARCH for Diabetes in Youth is a six-center, population-based study focusing on physician-diagnosed diabetes in youth in the U.S. (9). SEARCH sought to identify all existing cases of diabetes in youth <20 years old in 2001 and all newly diagnosed cases subsequently. Youth were invited to a study visit while metabolically stable, defined as no episode of diabetic ketoacidosis during the previous month. The visit occurred after an overnight fast, and all medication except long-acting insulin was discontinued the night before.

From the [1]University of Colorado Health Sciences Center, Denver, Colorado; the [2]Wake Forest University School of Medicine, Winston-Salem, North Carolina; the [3]Department of Epidemiology, University of South Carolina, Columbia, South Carolina; the [4]Sansum Medical Research Institute, Santa Barbara, California; the [5]Centers for Disease Control and Prevention, Atlanta, Georgia; the [6]Children's Hospital Medical Center, Cincinnati, Ohio; the [7]Children's Hospital and Regional Medical Center, Seattle, Washington; the [8]Kaiser Permanente Center for Health Research Northwest/Hawaii, Portland, Oregon; the [9]Northwest Lipid Research Laboratories, University of Washington, Seattle, Washington; and the [10]National Institute of Diabetes, Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland.

Address correspondence and reprint requests to Dana Dabelea, MD, PhD, 4200 E. 9th Ave., Box C245, Denver, CO 80262. E-mail: dana.dabelea@uchsc.edu.

Received for publication 19 July 2005 and accepted in revised form 20 October 2005.

Abbreviations: FCP, fasting C-peptide; IA2, insulinoma-associated protein 2.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Characteristics of the 449 study participants by age-group at diagnosis*

	Age-group at diagnosis (years)				
	0–4	5–9	10–14	15–19	*P* value
n (%)	50 (11.1)	159 (35.4)	189 (42.1)	51 (11.4)	
Diabetes duration (months)	7.7 ± 2.7	7.6 ± 2.7	7.6 ± 2.7	7.3 ± 2.5	0.3
Insulin dose (units · kg^{-1} · day^{-1})	0.6 ± 0.6	0.6 ± 0.2	0.6 ± 0.4	0.5 ± 0.2	0.6
FCP (ng/ml)	0.35 ± 0.26	0.52 ± 0.47	1.01 ± 1.09	1.69 ± 1.53	<0.0001
A1C (%)	8.0 ± 1.0	7.5 ± 1.3	7.5 ± 1.5	6.9 ± 1.4	0.002
Fasting blood glucose	183.4 ± 85.6	164.8 ± 76.7	173.8 ± 80.0	155.2 ± 65.0	0.5
GAD65 titer	0.61 ± 1.44	0.55 ± 0.95	0.43 ± 0.54	0.40 ± 0.45	0.1
IA2 titer	0.47 ± 0.41	0.58 ± 0.52	0.57 ± 0.43	0.38 ± 0.45	0.2
% 1:2 DA positive	44:56	1:49	45:55	63:37	0.5

Data are means ± SD unless otherwise indicated. *P* values are from testing the correlation between each variable and continuous age at diagnosis; for %1:2 diabetes antoantibody (DA) positive, Spearman's rank correlation, using continuous age at diagnosis vs. the number of positive DAs, was used to assess significance.

Blood specimens were processed locally and shipped within 24 h to the central laboratory. Samples were analyzed for GAD65 and insulinoma-associated protein 2 (IA2) diabetes autoantibodies in radioligand-binding assays (12). The levels were expressed as relative indexes, using positive and negative control samples. The positive control sample was the World Health Organization standard for islet cell antibodies. The negative control samples were prepared from a pool of normal sera. A signal-to-noise ratio of ≥10 was required. Fasting C-peptide (FCP) was measured by radioimmunoassay (13). Assay precision was excellent, with a coefficient of variance between 6.6 and 10.7% and a sensitivity limit of 0.15 ng/ml.

The average of two weight and height measurements was used to calculate BMI (weight in kilograms divided by the square of height in meters). Self-reported birth weight was obtained from mothers of the study participants. Maternal recall of birth weights of their children is considered to be reasonably accurate (14). Weight and height were compared with standards published by the National Center for Health Statistics (15). This allows each individual's deviation from the reference value to be calculated in terms of a normalized SD score (SDS) (*z* score).

The study group included all patients aged <20 years with newly diagnosed diabetes between 2001 and 2004 who had positive results for diabetes autoantibodies (either GAD65 or IA2) measured at a research visit 3–12 months after diagnosis ($n = 449$). To minimize error due to dehydration at presentation, subjects whose research visit occurred <3 months from the clinical diagnosis of diabetes were excluded ($n = 164$).

Statistical analyses

All statistical analyses were conducted using SAS version 8.2. The relationships between age at diagnosis of type 1 diabetes and both BMI and birth weight SDSs were first explored in univariate analyses looking for both linear and nonlinear associations. Multiple linear regression analyses, with age at diagnosis as the dependent variable, were conducted separately to explore the relationship with BMI SDS and the relationship with birth weight SDS, after controlling for each other and for other potential confounding variables (diabetes duration, sex, race/ethnicity, and FCP levels). To test the hypothesis that an intensified autoimmune response mediates the associations of interest, a series of linear regression models were fit, regressing in model 1 age at diagnosis on explanatory variables (BMI SDS or birth weight SDS), as detailed above, and in model 2 age at diagnosis on both mediator (diabetes autoantibodies number/titers) and explanatory variables. A change in the estimate of the effect of BMI SDS or birth weight SDS on age at diagnosis from model 1 to 2 was considered evidence of mediation (16). Because a significant interaction between BMI SDS and FCP on age at diagnosis was noted, the relationship between BMI SDS and onset age was further explored, stratified by FCP levels. Because BMI was measured at variable intervals from diagnosis (from 3 to 12 months, 7.6 ± 2.7 [mean ± SD]), all models were adjusted for the duration of diabetes from onset to BMI measurement. All analyses were also repeated in strata of diabetes duration (3–6 months [$n = 186$ subjects], 5–9 months [$n = 131$ subjects], and 9–12 months [$n = 132$ subjects]).

RESULTS — A total of 449 youths (231 boys and 218 girls, 74% non-Hispanic white) with new-onset diabetes at age <20 years (mean age 9.6 years) and positive results for diabetes autoantibodies were included. Of the participants, 51% had positive results for both GAD65 and IA2 autoantibodies and 49% had positive results for one type of diabetes autoantibody only, usually GAD65. Of the participants, 50% had FCP values <0.5 ng/ml and 20% undetectable FCP values (≤0.15 ng/ml). Mean ± SD BMI SDS was 0.7 ± 1.1 and birth weight SDS was 0.03 ± 1.2.

Characteristics of study participants are presented in Table 1 and suggest that this population is typical of youths with type 1 diabetes. Importantly, duration of diabetes from onset to the research visit was similar in all age-groups. Younger participants had lower FCP ($P < 0.0001$) and higher HbA_{1c} levels (A1C) ($P < 0.002$ for trend) than older subjects, but no significant pattern with age in terms of diabetes autoantibody number/titers was noted. Blood glucose levels were similar, suggesting that age-related FCP differences are not due to glucotoxicity but rather reflect more aggressive β-cell destruction in younger youth.

Figure 1 shows the mean age at diagnosis of type 1 diabetes by quartiles of BMI SDS (*A*) and quartiles of birth weight SDS (*B*). The hypothesized association of younger age at onset with increasing BMI was not observed ($P = 0.14$ for linear trend), and nonlinear associations were not significant. A significant association between lower birth weight SDS and younger age at diagnosis was noted ($P = 0.002$). No associations were found between onset age and height or weight change since birth (data not shown).

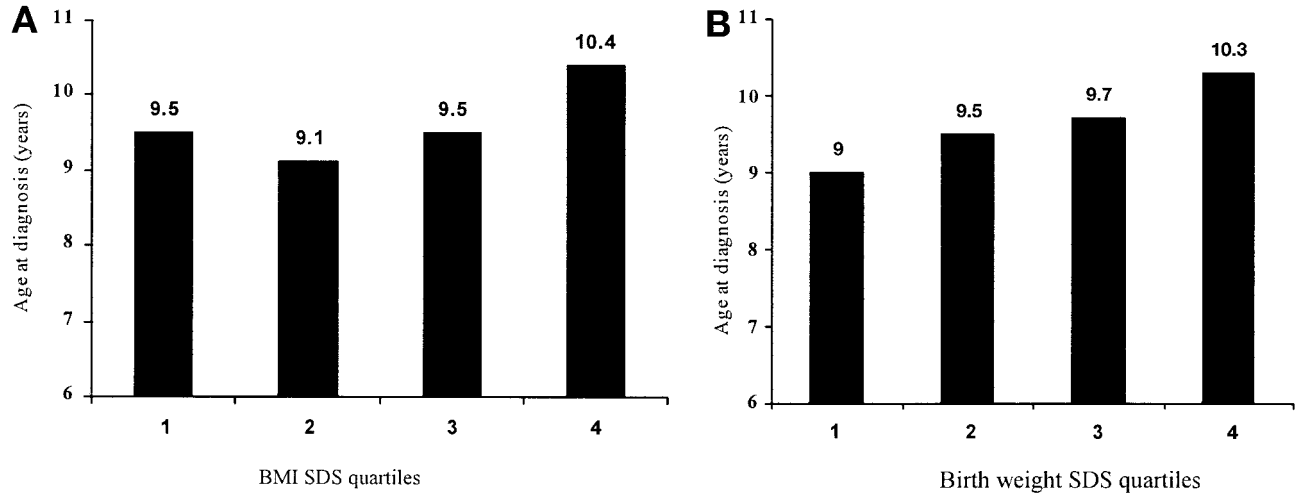

Figure 1—*Age at diagnosis of type 1 diabetes by quartiles of BMI SDS* (A) *and quartiles of birth weight SDS* (B). *Quartiles are numbered from 1 (lowest) to 4 (highest).* A: *Means ± SD (ranges) for BMI SDS are as follows: quartile 1, −0.7 ± 0.6 (−3.5 to −0.04); quartile 2, 0.4 ± 0.2 (−0.04 to 0.8); quartile 3, 1.1 ± 0.2 (0.8–1.4); and quartile 4, 2.0 ± 0.5 (1.4–4.7).* P *(trend) = 0.14 for the association between age at diagnosis and BMI SDS.* B: *Means ± SD (ranges) for birth weight SDS are as follows: quartile 1, −1.5 ± 0.7 (−3.6 to −0.7); quartile 2, −0.3 ± 0.2 (−0.7 to 0.01); quartile 3, 0.3 ± 0.2 (0.01–0.7); and quartile 4, 1.6 ± 0.7 (0.7–3.9).* P *(trend) = 0.002 for the association between age at diagnosis and birth weight SDS.*

BMI SDS was not a determinant of age at onset, even when controlled for potential confounders (Table 2, model 1). Similar results were noted in stratified analyses by sex, ethnicity (non-Hispanic white/other), and diabetes duration (data not shown). An interaction between diabetes duration and BMI SDS on age at onset was tested and found not to be significant. There was a very strong interaction (model 2) between BMI SDS and FCP on age at diagnosis ($P < 0.0001$), suggesting that the relationship between BMI and onset age is modified by FCP level: the lower the β-cell function, the stronger an inverse relationship between BMI and onset age. The interaction between FCP and BMI SDS on onset age was observed in all diabetes duration strata (3–6 months, $P = 0.01$; 6–9 months, $P = 0.005$; 9–12 months, $P = 0.02$), suggesting that the effect of FCP on the relationship between BMI and onset age is similar for participants whose research visit occurred anytime between 3 and 12 months from diagnosis.

In addition, when controlling for potential confounders, birth weight SDS was still a significant predictor of age at onset of type 1 diabetes, independent of current BMI SDS (model 1) and FCP level (model 2). A decrease of 1 SDS in birth weight (639 g) was associated with an ~5-month earlier presentation with diabetes.

In model 3 (Table 2), we examined whether addition of the proposed mediator altered the relationships between BMI SDS or birth weight SDS and age at onset of diabetes. None of the regression coefficients for the relationships of interest in model 2 were altered by the addition of diabetes autoantibody number in model 3. Identical results were obtained when diabetes autoantibody number was replaced with diabetes autoantibody titers.

Figure 2 shows the relationship between BMI SDS and age at diagnosis, stratified by FCP levels and adjusted for sex, race/ethnicity, birth weight, diabetes duration, and number of positive diabetes autoantibodies. Among subjects with

Table 2—*Association between age at diagnosis of type 1 diabetes and predictor variables in sequential multiple linear regression analysis models*

	Model 1		Model 2		Model 3	
	Estimate	*P*	Estimate	*P*	Estimate	*P*
BMI SDS	1.3	0.51	2.2	0.4	2.3	0.3
Birth weight SDS	5.3	0.004	5.5	0.0009	5.5	0.001
Sex						
Girls vs. boys	−6.8	0.1	−3.6	0.3	−3.7	0.3
Ethnicity						
Non-Hispanic white vs. other	−9.0	0.06	−3.2	0.5	−3.2	0.5
Diabetes duration	−0.9	0.3	0.3	0.7	0.3	0.7
FCP (per 1 ng/ml)			41.9	<0.0001	42.0	<0.0001
BMI SDS*FCP			−11.1	<0.0001	−11.1	<0.0001
Diabetes autoantibody number (1 vs. 2)					−1.8	0.6

Model 1: adjusted for birth weight, sex, race/ethnicity, and diabetes duration. Model 2: model 1 + FCP and BMI SDS*FCP interaction. Model 3 (explains 35% of variability in age at diagnosis): model 2 + number of positive diabetes antibodies. Coefficients can be interpreted as months of age; if the coefficient is negative, the association is with younger onset in months.

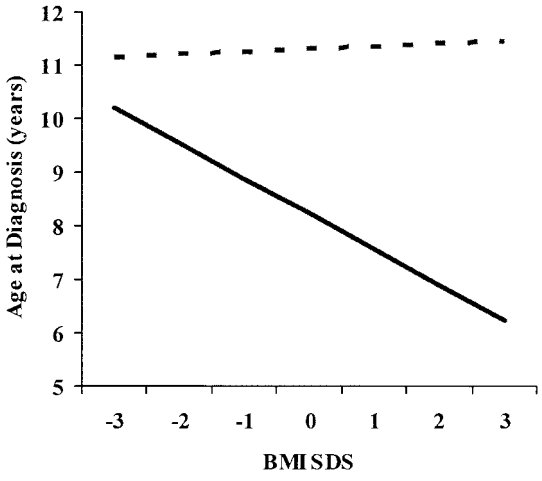

Figure 2—*The relationship between BMI SDS and age at diagnosis of type 1 diabetes by FCP levels (below and above the median) from two multiple linear regression models, adjusted for sex, race/ethnicity, birth weight SDS, diabetes duration, and number of positive diabetes autoantibodies. FCP median is 0.5 ng/ml. P < 0.0001 for the interaction between BMI SDS and FCP on age at onset. - - - -, FCP ≥ median; ——, FCP < median.*

FCP below the median (<0.5 ng/ml) an inverse association was found (regression coefficient: −7.9, $P = 0.003$). Inclusion of diabetes autoantibody titers or number of positive diabetes autoantibodies in these models did not alter the relationship of interest. This suggests that the inverse association between BMI SDS and onset age observed in subjects with reduced β-cell function is not mediated through an intensified autoimmune process.

For patients with FCP above the median no association emerged between BMI SDS and onset age (regression coefficient 0.5, $P = 0.8$). Further adjustment for differences in FCP levels within this group did not change this finding.

CONCLUSIONS — Among U.S. youth with newly diagnosed autoimmune diabetes, the hypothesized inverse relationship between BMI and onset age is present only among subjects with reduced FCP levels (Fig. 2). These patients have compromised pancreatic β-cell function and can no longer compensate for the additional metabolic demands associated with higher BMI. Whether the reduced β-cell function is solely due to an autoimmune-mediated attack or whether nonautoimmune factors also contribute is a distinction that we are unable to make in this study. Our data suggests that "acceleration" occurs late during the natural evolution of type 1 diabetes, when β-cell function is already compromised by an autoimmune attack.

The other 50% of participants had relatively preserved β-cell function (≥0.5 ng/ml), despite having autoimmune diabetes. This group was older ($P < 0.001$) and had higher BMI SDS ($P < 0.001$) but diabetes autoantibody levels/numbers similar to those for the group presenting with low FCP. In this group, the statistical association between BMI and onset age was not apparent. Although the reason for this finding is not clear, it is possible that diabetes was diagnosed in these patients before complete decompensation could occur. Importantly, duration of diabetes from onset to the research visit was similar in the group presenting with FCP above and below the median (7.3 vs. 7.9 months).

Data from Middlesbrough, U.K., showed a relationship between younger age at diagnosis of type 1 diabetes and higher BMI (17), but the relationship was not replicated among children from Birmingham, U.K (18). These U.K. studies involved a similarly small number of patients (94 and 95, respectively) with similar age and sex ratios. Both U.K. studies lacked serologic data, and neither assessed residual insulin secretion. By contrast, SEARCH participants were typed according to a biochemical algorithm, and FCP was used as a marker of residual insulin secretion. Beyond simply replicating the previous studies, our data show that the association between BMI and age at onset is observed only among subjects with substantially reduced β-cell function. This may explain the conflicting results from previous studies that did not measure residual insulin secretion.

Metabolically upregulated β-cells in obese persons can be destroyed through autoimmune (8) and nonautoimmune (19) mechanisms that can occur independently or in concert, as predicted by the subjects' genetic makeup. Our results suggest that the association between BMI and age at onset of type 1 diabetes observed among youth with reduced β-cell function is not mediated through an intensified autoimmune response, at least as reflected by higher number or titers of positive diabetes autoantibodies. In support of this statement, no association was noted between BMI SDS and GAD65 antibody level, and a significant but weak correlation ($r = 0.04$, $P = 0.05$) was found between BMI SDS and IA2 antibody level.

The other main finding of this study is that lower birth weight may accelerate the type 1 diabetes onset. Khan and Couper (20) also noted that low birth weight infants (<2.5 kg) showed an earlier age at onset of type 1 diabetes. Similarly, Kibirige et al. (17) found a trend of younger onset age with lower birth weight among U.K. youths with type 1 diabetes. The association between lower birth weight and younger age at onset does not seem to be accounted for by increased β-cell autoimmune destruction, and no correlation was found between birth weight and diabetes autoantibody titers. Lower birth weight could be a marker of fetal exposures that result in either increased insulin resistance or reduced pancreatic β-cell mass later in life. Alternatively, certain genes may be associated with both reduced fetal growth and later risk of type 1 diabetes (21). Whether the association between lower birth weight and younger onset age is a consequence of fetal environment, inherited susceptibility genes, or both requires further investigation.

This study has several limitations. Most important, the cross-sectional design precludes conclusions about causality or the order of events. BMI was measured after the diagnosis of diabetes, at variable intervals within the 1st year, as were FCP and diabetes autoantibodies. To minimize error due to the presumed weight loss associated with diabetes onset, we restricted the analyses to youth examined between 3 and 12 months after diagnosis, when stable growth trajectories are likely to have been reestablished. In addition, we controlled for diabetes duration, we ruled out a potential interaction between diabetes duration and BMI on onset age, and we noted identical results in analyses stratified by diabetes duration. We thus conclude that our findings are not influenced by the fact that BMI was obtained at variable time intervals after diagnosis. Recent studies also suggest that β-cell function and diabetes autoantibody positivity (22,23) are fairly stable within the 1st year after diagnosis. Another limitation is the absence of information on length of gestation, which may have

helped the interpretation of the relationship between birth weight and onset age.

Longitudinal studies using serial measurements of diabetes autoantibodies, BMI, insulin resistance, and insulin secretion before diabetes onset, in addition to HLA genotype, are needed to fully explore the accelerator hypothesis. They will also shed light on the likely mechanism(s) and critical period(s) during the pre-diabetes state, by which and when increased insulin resistance may "accelerate" the type 1 diabetes process. Recently, the Melbourne Pre-Diabetes Study (11) reported that diabetes autoantibody-positive relatives of type 1 diabetes probands who progress most rapidly to diabetes have greater insulin resistance for their level of insulin secretion. Our finding that BMI is associated with an earlier presentation of type 1 diabetes only when FCP is substantially reduced is consistent with the Australian data.

In summary, among U.S. youths, increasing BMI appears to accelerate the disease process leading to type 1 (autoimmune) diabetes only among individuals with reduced β-cell function, which can no longer compensate for the increasing demands associated with larger body size. The importance of this finding at the individual level is still to be determined; however, the increasing prevalence of childhood obesity (24) may substantially account for the younger age at onset of type 1 diabetes observed in various populations. Lower birth weight also accelerates the disease process, suggesting that the intrauterine environment may be a determinant of age at onset of type 1 diabetes.

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