

Clinical Research Article

Factors Associated With the Decline of C-Peptide in a Cohort of Young Children Diagnosed With Type 1 Diabetes

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Abbreviations: AUC, area under the curve; CI, confidence interval; BMI, body mass index; FDR, first-degree relative; HbA1c, hemoglobin A1c; HLA, human leukocyte antigen; JDRF, Juvenile Diabetes Research Foundation; SD, standard deviation; SEARCH, SEARCH for Diabetes in Youth study; TEDDY, The Environmental Determinants of Diabetes in the Young; T1D, type 1 diabetes.

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Abstract

Context: Understanding factors involved in the rate of C-peptide decline is needed to tailor therapies for type 1 diabetes (T1D).

Objective: Evaluate factors associated with rate of C-peptide decline after a T1D diagnosis in young children.

Design: Observational study.

Setting: Academic centers.

Participants: A total of 57 participants from the Environmental Determinants of Diabetes in the Young (TEDDY) study who were enrolled at 3 months of age and followed until T1D, and 56 age-matched children diagnosed with T1D in the community.

Intervention: A mixed meal tolerance test was used to measure the area under the curve (AUC) C-peptide at 1, 3, 6, 12, and 24 months postdiagnosis.

Outcome: Factors associated with rate of C-peptide decline during the first 2 years postdiagnosis were evaluated using mixed effects models, adjusting for age at diagnosis and baseline C-peptide.

Results: Adjusted slopes of AUC C-peptide decline did not differ between TEDDY subjects and community controls ($P = 0.21$), although the former had higher C-peptide baseline levels. In univariate analyses combining both groups ($n = 113$), younger age, higher weight and body mass index z-scores, female sex, an increased number increased number of islet autoantibodies, and IA-2A or ZnT8A positivity at baseline were associated with a higher rate of C-peptide loss. Younger age, female sex, and higher weight z-score remained significant in multivariate analysis (all $P < 0.02$). At 3 months after diagnosis, higher HbA1c became an additional independent factor associated with a higher rate of C-peptide decline ($P < 0.01$).

Conclusion: Younger age at diagnosis, female sex, higher weight z-score, and HbA1c were associated with a higher rate of C-peptide decline after T1D diagnosis in young children.

Freeform/Key Words: C-peptide, pediatric type 1 diabetes, new onset, beta cell decline, risk factors

Type 1 diabetes (T1D) is an autoimmune disease resulting from the progressive immune-mediated destruction of beta cells. Clinical trials employing immunotherapies in T1D have sought to prevent beta cell loss at each of Stage 1, 2, and 3 of the disease (ie, both before and after clinical diagnosis) (1). Preservation of beta cell function has been associated with lower risk of hypoglycemia and lower risk of long-term complications such as microalbuminuria and retinopathy (2, 3). Notably, clinical trials using rituximab (anti-CD20), abatacept (CTLA4-Ig), alefacept (anti-CD2), teplizumab (anti-CD3), and low-dose antithymocyte globulin (ATG) (4–8) have demonstrated transient preservation of C-peptide in new onset T1D. In addition, teplizumab recently demonstrated the ability to delay, by more than 2 years, progression from Stage 2 to Stage 3 T1D in high-risk subjects (9). In double islet autoantibody positive subjects with first phase insulin below the threshold, oral insulin immunomodulation delayed progression to Stage 3 by 2 years (10). Improved understanding of the factors involved in the rate of C-peptide decline could help tailor immunomodulatory therapies to specific groups or subjects and increase the success rates of these clinical trials (11).

An older age and a higher body mass index (BMI) have been previously associated with higher C-peptide levels at diagnosis of T1D (12, 13). The decline in stimulated C-peptide during the first year after the diagnosis has been highly variable, from 0% to 58% (14, 15), and factors involved in this variability are still only partially understood. While older age, lower HbA1c, and higher BMI at diagnosis have been reported to predict a slower loss of C-peptide (16–18), the SEARCH study showed a progressive decline in beta cell function independent of age, sex, HbA1c, and BMI (19).

Children participating in prospective studies, such as the Environmental Determinants of Diabetes in the Young (TEDDY) study, typically have a less severe clinical presentation at diabetes onset, with less diabetic ketoacidosis and diabetes symptoms (20, 21). We have previously shown that children diagnosed through the TEDDY study have higher C-peptide levels at onset compared with community-diagnosed children, and their C-peptide levels stayed higher throughout the first 12 months following the onset of diabetes (22). The goal of the current study was to evaluate factors associated with the rate of C-peptide decline in the first 2 years after the diagnosis of clinical T1D in a cohort of young children.

Materials and Methods

Study population

From September 2004 to February 2010, the TEDDY study identified 8676 infants at increased risk for T1D through genetic screening for diabetes-susceptible HLA DR-DQ genotypes at sites in Sweden, Finland, Germany, Colorado, Washington State, and Florida/Georgia. Those enrolled are followed prospectively from birth to 15 years of age, with study visits beginning at 3 months of age, then every 3 months until 4 years of age, then every 6 months thereafter. Children positive for islet autoantibodies are followed every 3 months. The details of screening and follow-up have been previously published (23, 24). The JDRF follow-up study recruited TEDDY study children diagnosed with T1D from January 2012 to December 2016; a total of 161 TEDDY study children were diagnosed with T1D during that time. For this study, 70 TEDDY study children and 60 age-matched children diagnosed with T1D

from the community were enrolled by December 2016. Among the 130 enrolled subjects, 113 subjects had complete C-peptide baseline data available and were therefore included in the analysis. Control subjects from the community were matched to TEDDY subjects by age of diabetes diagnosis within 1 year and were required to have at least 1 positive islet autoantibody at diagnosis. Type 1 diabetes was defined according to American Diabetes Association criteria for diagnosis (25).

After diagnosis of T1D, all participants had visits with HbA1c and a mixed meal tolerance test (MMTT) within 1 month of onset, then at 3, 6, and 12 months after diagnosis, and biannually thereafter. The primary outcome measure was the area under the curve (AUC) for serum C-peptide in response to a 2-hour MMTT. The goal was to follow all subjects for at least 2 years after diagnosis or until the loss of detectable endogenous C-peptide. Parents (or legal guardian) of the subjects provided written informed consent, and the children assent when applicable. The study was approved by the ethical review boards of all participating institutions.

Study visits

Subjects came in fasting for MMTT, which consisted of a standardized liquid meal, Boost High Protein (Nestle Health Care Nutrition, Inc., Bridgewater, New Jersey) given at 6 ml/kg to a maximum of 360 ml. HbA1c was measured by a Tosoh G8 HPLC Analyzer (Tosoh Bioscience Inc., San Francisco, California) at the Diabetes Diagnostic Laboratory at the University of Missouri, Columbia. C-peptide (ng/ml) was measured using Tosoh reagents on a TOSOH 2000 autoanalyzer (Tosoh Bioscience Inc., San Francisco, California) at the Northwest Lipid Research Laboratories at the University of Washington.

Islet autoantibodies

Autoantibodies to GAD65, IA-2, and ZnT8 were measured in 2 reference laboratories by standard radiobinding assays (26). For sites in the United States, all serum samples were assayed at the Barbara Davis Center for Diabetes at the University of Colorado. In Europe, all sera were assayed at the University of Bristol, United Kingdom. Both laboratories have previously shown high assay sensitivity and specificity, as well as concordance (27). Positive samples were reanalyzed in the other laboratory for confirmation (US samples in Europe and vice versa).

Statistical analysis

Data were analyzed using the Statistical Analysis System software (version 9.4; SAS Institute, Cary, North Carolina). C-peptide was measured at time points 0, 15, 30, 60, 90,

and 120 minutes. These timed values were combined using the trapezoidal rule to approximate the AUC; the reported value is the AUC divided by 120 minutes, which is an estimate of the mean of the C-Peptide level over the 2-hour period. Insulin-dose adjusted HbA1c (IDAA1C), an alternate measure of residual beta cell function (28), was calculated as $\text{HbA1c (\%)} + (4 \times \text{insulin dose (units/kg/day)})$.

Mixed-effects models were used to analyze the longitudinal data of C-peptide AUC, where AUC C-peptide values were normalized using a log-transformation on the value in the unit of ng/mL plus 1 ($\log(x + 1)$). The matching of case-control was modeled as a random effect and within-subject correlation was modeled using a first-order autoregressive structure. The time from diagnosis (months) was a covariate in the models and its corresponding coefficient was interpreted as the slope of C-peptide AUC change from diagnosis (ie, the negative value of the rate of C-peptide AUC loss). The effect of a potential factor on the rate of C-peptide AUC loss was modeled by examining an interaction term between the factor and the time from diagnosis. All the analyses were adjusted for age at diagnosis (years), C-peptide AUC at baseline, and the factor being examined. C-peptide AUC at baseline and autoantibody status (number of positive autoantibodies) were the measure from the baseline visit or from the 3-month visit if the baseline data was missing.

The effect of each of the potential factors on the rate of C-peptide AUC loss was examined individually. Factors with $P < 0.05$ for their effects on the slope were further analyzed in multivariate analysis using backward elimination procedure. In the backward elimination procedure, factors having effects on the rate of C-peptide AUC loss with $P > 0.10$ were eliminated. All participants with missing data specified as part of a particular analysis were omitted from that analysis. Two-tailed P -values < 0.05 were considered to be statistically significant.

Results

Characteristics at diagnosis of diabetes of the 57 TEDDY study and 56 community control children are described in Table 1. Mean age of diagnosis was 6.5 ± 1.8 years in these children and did not differ between TEDDY cases and community controls. As expected, the TEDDY study children had a higher frequency of the high-risk HLA DR3/4 genotype (56% vs 18%, $P < 0.001$). None of the TEDDY study children presented with diabetic ketoacidosis (DKA) at diagnosis, while 16% of the community children did ($P = 0.001$), with an overall low frequency of DKA for this cohort of young children. The low rate of DKA in the community group could potentially be explained by the willingness of more medically aware or

committed community control families to enroll in this intensive follow-up study with multiple MMTTs during the 1st year postdiagnosis. The mean weight and BMI z-scores were higher at diagnosis in TEDDY study children versus community controls (0.6 vs 0.1, $P = 0.02$ and 0.2 vs -0.4, $P = 0.01$, respectively). TEDDY study children had a lower HbA1c at diagnosis and higher C-peptide

AUC at baseline than community controls (6.9% [52 mmol/mol] vs 10.2% [88 mmol/mol], $P < 0.001$ and 1.7 ng/mL vs 1.3 ng/mL, $P = 0.007$, respectively).

Individual trajectories of AUC C-peptide over time in TEDDY study children and community controls are shown in Fig. 1. The slope of the C-peptide AUC change was -0.030 per month overall (95% CI: -0.033, -0.028) in log scale, adjusted for age at diagnosis and AUC C-peptide at baseline. Adjusted slopes of C-peptide AUC change did not differ between TEDDY study subjects and community controls (slope = -0.032 vs. -0.029 per month, respectively, $P = 0.208$).

The following factors were examined for association with the rate of C-peptide loss: sex, first-degree relative with T1D, HLA DR3-DQ2/DR4-DQ8 genotype, age at diagnosis, presence of DKA, and/or diabetes symptoms at diagnosis as well as HbA1c, weight, height, and BMI z-scores at diagnosis. Additional factors from the baseline and 3-month visits included autoantibody status (IA-2A, GADA, and ZnT8A), C-peptide, HbA1c, and insulin dose-adjusted HbA1c. In univariate analyses at baseline, C-peptide, female gender, younger age, higher weight, and BMI z-scores as well as an increased number of autoantibodies, presence of IA-2A or ZnT8A autoantibodies were all associated with a higher rate of C-peptide loss; only factors that were significantly associated with a higher rate of C-peptide loss are shown in Table 2. Three of these 8 factors remained significant in multivariate analysis adjusted for C-peptide at baseline: younger age at diagnosis, female gender, and higher weight z-score (all $P < 0.02$, Table 3).

The same univariate and multivariate analyses at 3 months after diagnosis are shown in Tables 4 and 5. At that time point, C-peptide, female gender, younger age, higher weight and BMI, an increased number of autoantibodies, IA-2A positivity and ZnT8A positivity as well as higher HbA1c were all associated with a higher rate of C-peptide

Table 1. Characteristics of study participants

	TEDDY Case (N = 57)	Control (N = 56)	P-value ^a
Female, N (%)	25 (43.9)	30 (53.6)	0.349
FDR with T1D, N (%)	9 (15.8)	5 (8.9)	0.393
HLA DR3/4, DQB1*0302, N (%)	32 (56.1)	10 (17.9)	<0.001
Age at Diagnosis (years)	6.4 ± 1.8	6.7 ± 1.9	0.378
Diabetic ketoacidosis, N (%)	0 (0.0)	9 (16.1)	0.001
Weight z-score at diagnosis	0.6 ± 0.9	0.1 ± 0.9	0.021
Height z-score at diagnosis ^b	0.8 ± 1.0	0.6 ± 1.0	0.208
BMI z-score at diagnosis ^b	0.2 ± 1.1	-0.4 ± 1.2	0.010
HbA1c at diagnosis ^c (%)	6.9 ± 1.5	10.2 ± 2.3	<0.001
HbA1c at diagnosis (mmol/mol)	52 ± 16	88 ± 25	–
Positive autoantibodies, ^d N (%)	–	–	1
0–1 Ab	14 (24.6)	13 (23.2)	–
≥2 Ab	43 (75.4)	43 (76.8)	–
AUC C-Peptide at baseline ^d (ng/mL)	1.7 ± 0.8	1.3 ± 0.6	0.007

Means ± standard deviations are shown unless specified otherwise. Weight, height, and BMI were converted to SD units (Z scores) using the CDC growth chart.

Abbreviations: Ab, autoantibodies; AUC, area under the curve; BMI, body mass index; FDR, first-degree relative; HbA1c, hemoglobin A1c; HLA, human leukocyte antigen; TEDDY, The Environmental Determinants of Diabetes in the Young; T1D, type 1 diabetes.

^aWilcoxon rank-sum test for continuous variables and Fisher's exact test for proportions.

^bEight subjects with missing information were omitted from the analysis.

^cOne subject with missing HbA1c was omitted from the analysis.

^dData from baseline visit and if missing from 3-month visit.

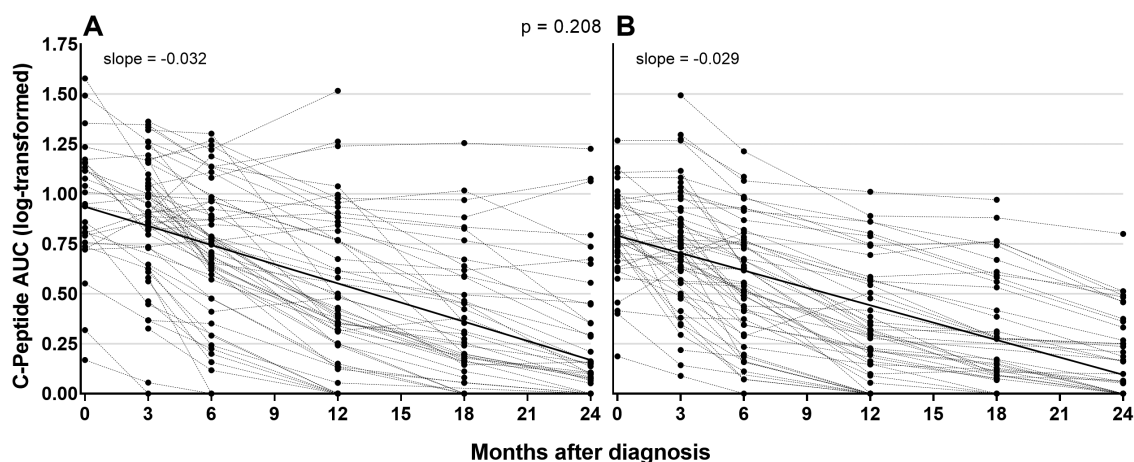


Figure 1. Individual trajectories of AUC C-peptide (log-transformed) over time in TEDDY children (A) and community controls (B). Abbreviation: AUC, area under the curve.

Table 2. Factors associated with slope of AUC C-peptide change (univariate baseline analyses)

Factor	Estimated Effect (95% CI) on the Slope of AUC C-peptide (ng/mL/month)	P-value
C-peptide AUC (per 1 unit log)	-0.011 (-0.021, -0.001)	0.037
Female sex	-0.006 (-0.011, -0.002)	0.010
Age at diagnosis (per year)	0.002 (0.000, 0.003)	0.008
Weight z-score at Dx (per SD)	-0.005 (-0.008, -0.002)	0.001
BMI z-score at Dx (per SD) ^a	-0.003 (-0.005, -0.001)	0.013
Number of positive autoantibodies	-0.006 (-0.009, -0.003)	<0.001
IA-2A positive	-0.009 (-0.015, -0.003)	0.004
ZnT8A positive	-0.007 (-0.012, -0.002)	0.009

A negative coefficient in these analyses corresponds to a faster rate of C-peptide loss. Analyses were adjusted for age at diagnosis (years) and C-peptide AUC at baseline.

Abbreviations: AUC, area under the curve; BMI, body mass index; CI, confidence interval; SD, standard deviation.

^aEight subjects with a missing BMI z-score were omitted from the analysis.

Table 3. Factors associated with slope of AUC C-peptide change (multivariate baseline analyses)

Factor	Estimated Effect (95% CI) on the Slope of AUC C-peptide (ng/mL/month)	P-value
Female	-0.006 (-0.011, -0.001)	0.014
Age at diagnosis (per year)	0.002 (0.001, 0.003)	0.005
Weight z-score at Dx (per SD)	-0.003 (-0.006, -0.001)	0.014
IA-2A positive	-0.006 (-0.012, 0.000)	0.061
ZnT8A positive	-0.005 (-0.010, 0.000)	0.065

A negative coefficient in these analyses corresponds to a faster rate of C-peptide loss. Analyses were adjusted for age at diagnosis (years) and C-peptide AUC at baseline.

Abbreviations: AUC, area under the curve; CI, confidence interval; SD, standard deviation.

loss (Table 4). In multivariate-adjusted analyses, higher HbA1c, in addition to younger age, female gender, and higher weight, was also associated with a higher rate of C-peptide decline (all $P < 0.02$, Table 5).

Discussion

In this international cohort of children diagnosed with T1D at a young age (mean age 6.5 years), we have analyzed factors involved in the rate of C-peptide decline during the first 2 years after the onset of disease. We

Table 4. Factors associated with slope of AUC C-peptide change (univariate 3 month visit analyses)

Factor	Estimated Effect (95% CI) on the Slope of AUC C-peptide (ng/mL/month)	P-value
C-peptide AUC (per 1 unit log)	-0.011 (-0.021, -0.001)	0.037
Female	-0.006 (-0.011, -0.002)	0.010
Age at diagnosis (per year)	0.002 (0.000, 0.003)	0.008
Weight z-score (per SD) ^a	-0.006 (-0.009, -0.002)	0.001
BMI z-score (per SD) ^a	-0.005 (-0.008, -0.002)	0.002
Number of positive autoantibodies ^b	-0.006 (-0.009, -0.003)	<0.001
IA-2A positive ^c	-0.010 (-0.016, -0.003)	0.002
ZnT8A positive ^c	-0.006 (-0.012, -0.001)	0.018
HbA1c (per %) ^d	-0.003 (-0.006, -0.001)	0.018

A negative coefficient in these analyses corresponds to a faster rate of C-peptide loss. Analyses were adjusted for age at diagnosis (years) and C-peptide AUC at baseline.

Abbreviations: AUC, area under the curve; BMI, body mass index; CI, confidence interval; HbA1c, hemoglobin A1c; SD, standard deviation.

^aThree subjects with missing information were omitted from the analysis.

^bSix subjects with missing information were omitted from the analysis.

^cFour subjects with missing information were omitted from the analysis.

^dThree subjects with missing HbA1c were omitted from the analysis.

Table 5. Factors associated with slope of AUC C-peptide change (multivariate 3 month visit analyses)

Factor	Estimated Effect (95% CI) on the Slope of AUC C-peptide (ng/mL/month)	P-value
Female	-0.006 (-0.010, -0.001)	0.017
Age at diagnosis (per year)	0.002 (0.001, 0.003)	0.001
Weight z-score (per SD)	-0.005 (-0.008, -0.001)	0.009
HbA1c (per %)	-0.004 (-0.007, -0.001)	0.005
IA-2A positive	-0.006 (-0.012, 0.000)	0.051
ZnT8A positive	-0.005 (-0.010, 0.000)	0.052

A negative coefficient in these analyses corresponds to a faster rate of C-peptide loss. Analyses were adjusted for age at diagnosis (years) and C-peptide AUC at baseline. Five subjects with missing information on HbA1c, IA-2A or ZnT8A status were omitted from the analysis.

Abbreviations: AUC, area under the curve; CI, confidence interval; HbA1c, hemoglobin A1c; SD, standard deviation.

have previously shown that children diagnosed through the TEDDY study have higher C-peptide levels at onset compared with community-diagnosed children and that C-peptide levels stay higher throughout the first 12 months following the onset of T1D (22). Here we found that rates of C-peptide AUC loss (slope), adjusted for age at diagnosis and C-peptide AUC at baseline, did not differ between

TEDDY study subjects and community controls, and that younger age at diagnosis, female sex, higher weight z-score, and higher HbA1c were associated with a faster decline of C-peptide over the first 2 years after diagnosis.

While age and BMI have been associated with C-peptide levels at diagnosis (13, 17, 18, 29), the rate of C-peptide decline after diagnosis has been highly variable in previous studies, and factors involved in the rate of C-peptide decline have not been consistent across studies. Data from 481 individuals with recent onset T1D enrolled in TrialNet studies showed that age at diagnosis and baseline C-peptide were significant predictors of the rate of C-peptide loss (11). A study looking at the rate of stimulated C-peptide decline in 446 children with new onset T1D from Scandinavia, Europe, and North America between 1982 and 2009 found that both the initial C-peptide and rate of C-peptide decline seemed to have increased over this 27-year time period (30). In that study, younger age, positivity for GADA, IAA, or both—but not BMI z-score, gender, or initial C-peptide—were associated with a faster rate of C-peptide decline during the 15 months after diagnosis. Of note, mean age varied from 9 years to 12.8 years for the 5 cohorts included, while this cohort of children was younger (mean age of 6.5 years at diagnosis). After adjusting for age at diagnosis and C-peptide AUC at baseline, IA-2A positivity and ZnT8A positivity in this study were associated with a higher rate of C-peptide loss in univariate analyses (<0.01), with $P = 0.06$ in multivariate analyses. Islet autoantibody positivity and levels have been shown to be associated with the rate of progression to T1D in children followed in prospective birth cohort studies such as TEDDY and the Diabetes Autoimmunity Study in the Young (31, 32). Therefore, it seems likely that ongoing autoimmunity as noted by autoantibody positivity would also play a role in rate of beta cell loss after diagnosis.

Preservation of C-peptide is known to be associated with a lower risk of hypoglycemia and a lower risk of long-term microvascular complications (2, 3). More recently, a study showed that DKA at diagnosis of T1D in children predicts persistently elevated HbA1c levels and poor long-term glycemic control independent of demographic and socioeconomic factors (33). In our current study, both higher HbA1c and a higher weight z-score were associated with a higher rate of C-peptide decline over the first 2 years after diagnosis, suggesting that metabolic factors could also play a role in the preservation of beta cell function. Diagnosis at a young age and poor metabolic control (higher HbA1c) could imply a more severe autoimmune process leading to an early presentation of the disease in those at risk. While some studies have reported preserved beta-cell function with a higher BMI close to diabetes onset (16), other studies have shown

greater C-peptide decline over 1 year postdiagnosis with a higher BMI (18, 34) or no effect of BMI on the rate of C-peptide decline postdiagnosis (17, 19). At diagnosis of diabetes in subjects <18 years old, HbA1c levels have been shown to inversely correlate with AUC C-peptide as well as measures of the timing of C-peptide responses in OGTT, including peak C-peptide and early and late C-peptide responses (35). These various metabolic measures are obviously intertwined, but may help develop endpoints for beta cell preservation trials and tailor therapies to specific individuals or groups of individuals.

Limitations of this study include a relatively small number of subjects diagnosed with T1D with follow-up limited to 2 years after diagnosis. This could influence the results of some of the factors that were borderline, such as IA-2A and ZnT8A positivity. In addition, as baseline visits happened about a month after diagnosis, IAA levels were not available for community control subjects and therefore could not be analyzed and were not included in the analysis of either group. Although the rate of C-peptide decline was not statistically different between the 2 groups, there are important differences between the groups, such as higher T1D genetic load and earlier diagnosis in TEDDY subjects. Therefore, it is possible that known or unknown factors that regulate beta cell function decline were different between these 2 groups.

In summary, this study of young children diagnosed with T1D shows that adjusted rates of C-peptide loss were similar between TEDDY study subjects and community controls. Younger age at diagnosis, female gender, a higher weight z-score, and a higher HbA1c were associated with a higher rate of C-peptide decline over the first 2 years after diagnosis, while positivity for IA-2A and ZnT8A autoantibodies might also contribute to C-peptide decline in young children.

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