Factors Associated with Decline of C-peptide in a Cohort of Young Children Diagnosed with 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 T1D diagnosis in young children.

Design: Observational study.

Setting: Academic centers.

Participants: 57 participants in The Environmental Determinants of Diabetes in the Young (TEDDY) 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 post-diagnosis.

Outcome: Factors associated with rate of C-peptide decline during the first 2 years post-diagnosis 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 BMI z-scores, female sex, increased number of islet autoantibodies, and IA-2A or ZnT8A positivity at baseline were associated

with 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 three months after diagnosis, higher HbA1c became an additional independent factor associated with 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 higher rate of C-peptide decline after T1D diagnosis in young children.

Keywords: C-peptide, pediatric type 1 diabetes, new onset, beta cell decline, risk factors

INTRODUCTION

Type 1 diabetes is an autoimmune disease resulting from the progressive immune-mediated destruction of beta cells. Clinical trials employing immunotherapies in type 1 diabetes have sought to prevent beta cell loss at each of stage 1, 2 and 3 of the disease, i.e. 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 anti-thymocyte globulin (ATG)(4-8) have demonstrated transient preservation of C-peptide in new onset type 1 diabetes. In addition, teplizumab recently demonstrated the ability to delay, by more than 2 years, progression from Stage 2 to Stage 3 type 1 diabetes in high-risk subjects(9). In double islet autoantibody positive subjects with first phase insulin below threshold, oral insulin immunomodulation delayed progression to stage 3 by two 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 BMI have been previously associated with higher C-peptide levels at diagnosis of type 1 diabetes(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),(17,18), 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) 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 to 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 type 1 diabetes 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 type 1 diabetes 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 children diagnosed with type 1 diabetes from January 2012 to December 2016; a total of 161 TEDDY children were diagnosed with type 1 diabetes during that time. For this study, 70 TEDDY children and 60 age-matched children diagnosed with type 1 diabetes in 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 one year and were required to have at least one positive islet

autoantibody at diagnosis. Type 1 diabetes was defined according to American Diabetes Association criteria for diagnosis(25).

After diagnosis of type 1 diabetes, all participants had visits with HbA1c and a Mixed Meal Tolerance Test (MMTT) within one month of onset, then at 3, 6, and 12 months after diagnosis, and bi-annually 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.) 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, CA) 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, CA) at the Northwest Lipid Research Laboratories at the University of Washington.

Islet Autoantibodies:

Autoantibodies to GAD65, IA-2, and ZnT8 were measured in two 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, NC). 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 HbA1c (%) + [4 x 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 (i.e., 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 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, TEDDY children had a higher frequency of the high-risk HLA DR3/4 genotype (56% vs 18%, p<0.001). None of the TEDDY 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 first year post-diagnosis. The mean weight and BMI z-scores were higher at diagnosis in TEDDY children vs community controls (0.6 vs 0.1, p=0.02 and 0.2 vs -0.4, p=0.01 respectively). TEDDY 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 children and community controls are shown in Figure 1. The slope of 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 subjects and community controls (slope=-0.032 vs. -0.029 per month respectively, p=0.208).

The following factors were examined for association with rate of C-peptide loss: sex, first-degree relative with type 1 diabetes, 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 months 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 increased number of autoantibodies, presence of IA-2A or ZnT8A autoantibodies were all associated with higher rate of C-peptide loss; only factors that were significantly associated with higher rate of C-peptide loss are shown in Table 2. Three of these eight 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, increased number of autoantibodies, IA-2A positivity and ZnT8A positivity as well as higher HbA1c were all associated with higher rate of C-peptide loss (Table 4). In multivariate adjusted analyses, higher HbA1c, in addition to younger age, female gender and higher weight, was also associated with higher rate of C-peptide decline (all $p < 0.02$, Table 5).

DISCUSSION

In this international cohort of children diagnosed with type 1 diabetes at a young age (mean age 6.5 years), we have analyzed factors involved in rate of C-peptide decline during the first 2 years after the onset of disease. We have previously shown that children diagnosed through the TEDDY study have higher C-peptide levels at onset compared to community-diagnosed children and that C-peptide levels stay higher throughout the first 12 months following the onset of type 1 diabetes(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 subjects and community controls, and that younger age at diagnosis, female sex, higher weight z-score and higher HbA1c were associated with 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), rate of C-peptide decline after diagnosis has been highly variable in previous studies and factors involved in rate of C-peptide decline have not been consistent across studies. Data from 481 individuals with recent onset type 1 diabetes enrolled in TrialNet studies showed that age at diagnosis and baseline C-peptide were significant predictors of rate of C-peptide loss (11). A study looking at rate of stimulated C-peptide decline in 446 children with new onset type 1 diabetes from Scandinavia, Europe and North America between 1982 and 2009 found that both 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 nor initial C-peptide, were associated with 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 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 rate of progression to type 1 diabetes in children followed in prospective birth cohort studies such as TEDDY and the Diabetes Autoimmunity Study in the Young (DAISY) (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 lower risk of hypoglycemia and lower risk of long-term microvascular complications(2,3). More recently, a study showed that diabetic ketoacidosis (DKA) at diagnosis of type 1 diabetes 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 higher weight z-score were associated with higher rate of C-peptide decline over the first 2 years after diagnosis, suggesting that metabolic factors could also play a role in 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 early presentation of the disease in those at risk. While some studies have reported preserved beta cell function with higher BMI close to diabetes onset(16), other studies have shown greater C-peptide decline over 1 year post-diagnosis with higher BMI(18,34) or no effect of BMI on the rate of C-peptide decline post-diagnosis(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 type 1 diabetes 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 two groups, there are important differences between the groups, such as higher type 1 diabetes 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 two groups.

In summary, this study of young children diagnosed with type 1 diabetes shows that adjusted rates of C-peptide loss were similar between TEDDY subjects and community controls. Younger age at diagnosis, female gender, higher weight z-score and higher HbA1c were associated with 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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[1]Ancillary Studies, [2]Diet, [3]Genetics, [4]Human Subjects/Publicity/Publications, [5]Immune Markers, [6]Infectious Agents, [7]Laboratory Implementation, [8]Psychosocial, [9]Quality Assurance, [10]Steering, [11]Study Coordinators, [12]Celiac Disease, [13]Clinical Implementation.

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Table 1: Characteristics of Study Participants

	TEDDY Case (N=57)	Control (N=56)	P value*
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‡	0.8 ± 1.0	0.6 ± 1.0	0.208
BMI z-score at diagnosis‡	0.2 ± 1.1	-0.4 ± 1.2	0.010
HbA1c at diagnosis# (%) HbA1c at diagnosis (mmol/mol)	6.9 ± 1.5 52 ± 16	10.2 ± 2.3 88 ± 25	<0.001
Positive autoantibodies§, N (%) 0-1 Ab|| ≥2 Ab	 14 (24.6) 43 (75.4)	 13 (23.2) 43 (76.8)	1
AUC¶ C-Peptide at baseline§ (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 CDC growth chart

* Wilcoxon rank-sum test for continuous variables and Fisher's exact test for proportions

† FDR with T1D= first-degree relative with type 1 diabetes

‡ Eight subjects with missing information were omitted from the analysis

One subject with missing HbA1c was omitted from the analysis

§ data from baseline visit and if missing from 3-month visit

|| Ab= autoantibodies

¶ 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)*	-0.003 (-0.005, -0.001)	0.013
# 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 (area under the curve) at baseline.

* Eight subjects with 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 (area under the curve) at baseline.

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)*	-0.006 (-0.009, -0.002)	0.001
BMI z-score (per SD)*	-0.005 (-0.008, -0.002)	0.002
# of positive autoantibodies †	-0.006 (-0.009, -0.003)	<0.001
IA-2A positive ‡	-0.010 (-0.016, -0.003)	0.002
ZnT8A positive ‡	-0.006 (-0.012, -0.001)	0.018
HbA1c (per %) §	-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 (area under the curve) at baseline.

* Three subjects with missing information were omitted from the analysis

† Six subjects with missing information were omitted from the analysis

‡ Four subjects with missing information were omitted from the analysis

§ Three 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 (area under the curve) at baseline.

Five subjects with missing information on HbA1c, IA-2A or ZnT8A status were omitted from the analysis.

Figure legends

Figure 1: Individual trajectories of AUC C-peptide (log-transformed) over time in TEDDY children (A) and community controls (B)

AUC= area under the curve

Figure 1