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ORIGINAL ARTICLE

Residual beta-cell function in diabetes children followed and diagnosed in the TEDDY study compared to community controls

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Objective: To explore whether children diagnosed with type 1 diabetes during islet autoantibody surveillance through The Environmental Determinants of Diabetes in the Young (TEDDY) study retain greater islet function than children diagnosed through the community.

Methods: TEDDY children identified at birth with high-risk human leukocyte antigen and followed every 3 months until diabetes diagnosis were compared to age-matched children diagnosed with diabetes in the community. Both participated in long-term follow up after diagnosis. Hemoglobin A1c (HbA1c) and mixed meal tolerance test were performed within 1 month of diabetes onset, then at 3, 6, and 12 months, and biannually thereafter.

Results: Comparison of 43 TEDDY and 43 paired control children showed that TEDDY children often had no symptoms (58%) at diagnosis and none had diabetic ketoacidosis (DKA) compared with 98% with diabetes symptoms and 14% DKA in the controls ($P < 0.001$ and $P = 0.03$, respectively). At diagnosis, mean HbA1c was lower in TEDDY (6.8%, 51 mmol/mol) than control (10.5%, 91 mmol/mol) children ($P < 0.0001$). TEDDY children had significantly higher area under the curve and peak C-peptide values than the community controls throughout the first year postdiagnosis. Total insulin dose and insulin dose-adjusted A1c were lower throughout the first year postdiagnosis for TEDDY compared with control children.

Conclusions: Higher C-peptide levels in TEDDY vs community-diagnosed children persist for at least 12 months following diabetes onset and appear to represent a shift in the disease process of about 6 months. Symptom-free diagnosis, reduction of DKA, and the potential for immune intervention with increased baseline C-peptide may portend additional long-term benefits of early diagnosis.

KEYWORDS

HbA1c, pediatric diabetes, preservation of C-peptide, prospective study, type 1 diabetes

1 | INTRODUCTION

Children participating in prospective studies, such as The Environmental Determinants of Diabetes in the Young (TEDDY), TrialNet, the Diabetes Autoimmunity Study in the Young (DAISY), BABYDIAB, and the Diabetes prediction in Skåne (DiPiS) study have been shown to have less diabetic ketoacidosis (DKA) and diabetes symptoms at diagnosis.[1–6] TEDDY follows children with serial longitudinal analysis of islet autoantibodies to insulin,[7] GAD65,[8] IA-2,[9] and ZnT8,[10] and for diagnosis of type 1 diabetes, and offers close monitoring for autoantibody-positive subjects through hemoglobin A1c (HbA1c) and oral glucose tolerance tests.[11] Although multiple autoantibody-positive subjects have a more than 80% risk of developing diabetes within 15 years, the rate of progression of these high-risk individuals varies significantly, from a few months to more than 10 years.[12,13]

Preservation of C-peptide has been associated with lower risk of hypoglycemia and lower risk of long-term complications such as microalbuminuria and retinopathy.[14,15] The decline in stimulated C-peptide during the first year after the diagnosis of type 1 diabetes, as reported in the literature, is highly variable from 0% to 58%.[16–19] Apart from early observational studies,[20] most of available C-peptide data are from the control arm of intervention trials. Data from subjects in TrialNet intervention studies (mean age 18 years) showed that 93% of type 1 diabetes patients still have detectable C-peptide at least 2 years from diagnosis.[21] Although these subjects were either placebo-treated subjects or subjects from intervention studies in which the intervention had no effect on beta-cell function, these study subjects had excellent diabetes control with mean HbA1c of 6.5% (48 mmol/mol) at entry and 7.6% (60 mmol/mol) after 2 years. To date, only 1 small study has looked at the natural history of C-peptide change in the general type 1 diabetes population.[22] In the latter study, the 9 children diagnosed through the DAISY study (mean age of diagnosis 12 years) had lower baseline HbA1c (6.5% vs 9.2%), lower insulin dose-adjusted HbA1c (IDAA1c: 7.4% vs 11.2%), and higher stimulated C-peptide at 60 minutes (2.5 ng/mL vs 1.6 ng/mL) when compared with 9 matched community children. However, those favorable patterns of IDAA1c and C-peptide were no longer apparent 1 year from diagnosis. Children followed before diabetes diagnosis within the DiPiS study had a lower HbA1c up to 2 years after diagnosis, compared with children diagnosed from the community.[4] In the T1D Exchange Clinic Network, the overall frequency of detectable

non-fasting C-peptide was 29%, with higher frequency in those diagnosed above age 18; residual secretion was present in almost 1 of 3 individuals 3 or more years from diabetes diagnosis.[23]

Although children are often diagnosed with type 1 diabetes with less severe presentation through TEDDY,[3,6] it is not known whether this close monitoring also leads to better outcomes beyond diagnosis. The goal of this study was to explore whether young children diagnosed with type 1 diabetes through the TEDDY study have higher C-peptide levels and less insulin needs during the first year after diagnosis compared with control children diagnosed through the community. This is the first large, prospective, age-matched effort to analyze preservation of C-peptide in young children from the general population in comparison to the TEDDY cohort.

2 | METHODS

2.1 | Study population

From September 2004 to February 2010, TEDDY accrued and followed initially a cohort of 8676 infants at increased genetic risk for type 1 diabetes. The vast majority (89%) have no first-degree relatives, while 11% are siblings or offspring of a person with type 1 diabetes. The participants were identified at birth 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.[24,25] The Juvenile Diabetes Research Foundation (JDRF) follow-up study has been recruiting TEDDY children diagnosed with type 1 diabetes since January 2012. As of November 2015, a total of 226 TEDDY subjects were diagnosed with diabetes, including 82 subjects since the start of this study (January 2012-November 2015); of these 82 eligible subjects, 59 enrolled into the JDRF follow-up study whereas 23 did not enroll. Among the 59 enrolled TEDDY subjects, 43 subjects had matched controls and were therefore included in the analysis. There were no significant differences in characteristics at diabetes diagnosis (age, gender, body mass index, family history of diabetes, diabetes symptoms, DKA, frequency of hospitalization, HbA1c, frequency of HLA-DR3/4,DQB1*0302 genotype, number of

positive autoantibodies, and mean autoantibody levels) between the eligible TEDDY children who enrolled into the JDRF follow-up study vs those who did not enroll (Table S1, Supporting Information). 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. Diabetes was defined according to American Diabetes Association criteria for diagnosis.[26] Family history in the JDRF follow-up study was collected at baseline visit for all controls, and for cases it was updated if it had not been updated within the previous 2 years in TEDDY.

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

2.2 | Study visits

Subjects came in fasting for MMTT, which consisted of a standardized liquid meal, Boost High Protein (Nestle Health Care Nutrition, Inc., Florham Park, New Jersey) given at 6 mL/kg to a maximum of 360 mL. The 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.) at the Northwest Lipid Research Laboratories at the University of Washington. The C-peptide assay is calibrated against the WHO IS 84/510 standard and has a sensitivity level of 0.02 ng/mL. Quality control samples with high, medium, and low C-peptide levels are analyzed several times per day to monitor the assay performance. The intra-assay coefficient of variation (CVs) for low and high C-peptide samples are 2.27% and 1.2% respectively. The inter-assay CVs for the low and high C-peptide samples are 3.1% and 2.42%, respectively. Blood glucose meter downloads were assessed to determine the average number of blood glucose tests performed daily.

2.3 | Islet autoantibodies

Autoantibodies to GAD65, IA-2, and ZnT8 were measured in 2 reference laboratories by standard radiobinding assays.[27] For sites in the United States, all serum samples were assayed at the Barbara Davis Center for Childhood Diabetes at the University of Colorado Denver. In Europe, all sera were assayed at the University of Bristol, UK. Both laboratories have previously shown high-assay sensitivity and specificity, as well as concordance.[28]

2.4 | Statistical analysis

Data were analyzed using the Statistical Analysis System software (version 9.4; SAS Institute, Cary, North Carolina). For the comparison of characteristics at diagnosis of diabetes, diabetes management, and

TABLE 1 Characteristics at diagnosis of diabetes in TEDDY cases vs community controls

	TEDDY (N = 43)	Community (N = 43)	P-value[3]
Age at diagnosis (y)			
Mean	6.0 ± 1.6	6.4 ± 1.8	0.001
Range	2.8-10.0	3.3-10.5	
Gender: female, N (%)	20 (47)	27 (63)	0.21
BMI[1]	16.0 ± 2.0	15.4 ± 2.5	0.26
Family history of diabetes, N (%)	9 (21)	2 (5)	0.04
Diabetes symptoms, N (%)	18 (42)	42 (98)	<0.001
Diabetic ketoacidosis, N (%)	0 (0)	6 (14)	0.03
Hospitalization at diagnosis, N (%)	21 (49)	32 (74)	0.01
HLA-DR3/4, DQB1*0302[1], N (%)	24 (56)	4 (10)	0.003
No. of positive autoantibodies[1,2], N (%)			
0	1 (4)	1 (3)	0.58
1	5 (19)	10 (30)	
≥2	21 (78)	22 (67)	
Mean GADA level[1,2]	0.55 ± 0.80	0.19 ± 0.59	0.07
Mean IA-2A level[1,2]	1.43 ± 0.83	1.35 ± 0.85	0.39
Mean ZnT8A level[1,2]	0.29 ± 0.20	0.23 ± 0.18	0.81
HbA1c[1], % (mmol/mol)	6.8 ± 1.3 (51 ± 14 mmol/mol)	10.5 ± 2.1 (91 ± 23 mmol/mol)	<0.001

Mean ± standard deviation are shown unless specified otherwise. Autoantibody levels were converted to SD units away from threshold (Z scores).

Abbreviations: BMI, body mass index; GADA, glutamic acid decarboxylase antibodies; HbA1c, hemoglobin A1c; TEDDY, The Environmental Determinants of Diabetes in the Young.

[1] Missing information in some subjects.

[2] Autoantibody data from baseline visit.

[3] P-values derived from paired t test for continuous variables and McNemar's test for proportions.

metabolic outcomes at each follow-up visit between cases and controls, paired analyses were used for confidence limits for continuous variables as the JDRF follow-up study has a 1:1 case-control matching design. 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. Both AUC and peak C-peptide values were log-transformed to make the values more normally distributed, and paired tests with adjustment for the difference of age at diagnosis between matched cases and controls were performed. The mean curves of log C-peptide AUC for cases and controls during the first 12 months were examined using the generalized estimating equation (GEE) method,[29] with adjustment for age at diagnosis. An exchangeable correlation structure was assumed to account for the correlation of repeated measures of C-peptide AUC at multiple follow-up visits for each subject over time and the empirical standard error estimates were used. Ninety-five percent confidence limits and P-values from the GEE analyses were based on the Wald test. Data were assumed to be missing at random and the observed data were analyzed. In addition, rates of C-peptide decline during the first year were calculated, adjusting for HLA-DR3/4,DQB1*0302 and age at diagnosis as these potential confounding factors were different between TEDDY cases and community controls. IDAA1c, an alternate measure of residual beta-cell function,[30] was calculated as HbA1c (%) + (4 × insulin dose [units/kg/d]). Two-tailed P-values less than 0.05 were considered to be statistically significant.

3 | RESULTS

Characteristics at diagnosis of diabetes of the 43 TEDDY and 43 community control children are described in Table 1. TEDDY children diagnosed with diabetes often had no symptoms (58%) and none (0%) had DKA, compared with 98% with diabetes symptoms and 14% DKA in the community controls ($P < 0.001$ and $P = 0.03$, respectively). TEDDY children had lower mean HbA1c at diagnosis (6.8%, 51 mmol/mol) compared with community control children (10.5%, 91 mmol/mol) ($P < 0.001$). By study design, TEDDY children were more likely to have the high-risk HLA-DR3/4, DQA1*05:01-B1*02:01/DQA1*03:01-B1*03:02 genotype and a positive family history of type 1 diabetes. Although this study did match on age of diagnosis within a year, TEDDY children were younger at diabetes onset (6.0 vs 6.4 years, $P = 0.001$), so C-peptide analyses were adjusted for age. The baseline visit occurred at a mean of 1.4 months after diabetes diagnosis (range: 0-2.7 months) and was similar between TEDDY cases and community controls (1.1 vs 1.6 months, respectively, $P = 0.07$). The number of positive islet autoantibodies, as well as levels of autoantibodies (GADA, IA-2A, and ZnT8A), were similar between the 2 groups.

C-peptide levels during the first year after diabetes diagnosis between the TEDDY and community children are shown in Table 2. TEDDY children had higher AUC and peak C-peptide values than community controls throughout the first year postdiagnosis; these

TABLE 2 Stimulated C-peptide levels at baseline, 3, 6, and 12 months

	TEDDY (N = 17) baseline	Community (N = 28) baseline	P-value	TEDDY (N = 33) 3 mo	Community (N = 34) 3 mo	P-value	TEDDY (N = 33) 6 mo	Community (N = 29) 6 mo	P-value	TEDDY (N = 31) 12 mo	Community (N = 24) 12 mo	P-value
AUC C-peptide ng/mL (pmol/mL)	1.6 ± 0.7 (0.5 ± 0.2)	1.2 ± 0.5 (0.4 ± 0.2)	0.15	1.5 ± 0.7 (0.5 ± 0.2)	1.2 ± 0.8 (0.4 ± 0.3)	0.045	1.2 ± 0.8 (0.4 ± 0.3)	0.6 ± 0.6 (0.2 ± 0.2)	0.008	0.8 ± 0.7 (0.3 ± 0.2)	0.3 ± 0.4 (0.1 ± 0.1)	0.008
Peak C-peptide ng/mL (pmol/mL)	2.1 ± 0.9 (0.7 ± 0.3)	1.6 ± 0.6 (0.5 ± 0.2)	0.15	1.9 ± 1.0 (0.6 ± 0.3)	1.5 ± 1.0 (0.5 ± 0.3)	0.025	1.5 ± 1.0 (0.5 ± 0.3)	0.8 ± 0.7 (0.2 ± 0.2)	0.007	1.0 ± 0.9 (0.3 ± 0.3)	0.3 ± 0.5 (0.1 ± 0.2)	0.01

Mean ± standard deviation are shown. P-values derived from paired tests adjusting for the difference of age at diagnosis between matched case-control.

Abbreviations: AUC, area under the curve; TEDDY, The Environmental Determinants of Diabetes in the Young.

TABLE 3 Diabetes management and other outcomes at baseline, 3, 6, and 12 months

	TEDDY (N = 37) baseline	Community (N = 35) baseline	Mean diff (95% CI)	TEDDY (N = 43) 3 mo	Community (N = 40) 3 mo	Mean diff (95% CI)	TEDDY (N = 42) 6 mo	Community (N = 38) 6 mo	Mean diff (95% CI)	TEDDY (N = 36) 12 mo	Community (N = 27) 12 mo	Mean diff (95% CI)
HbA1c,[1] % (mmol/mol)	6.3 ± 0.9 / 45 ± 10	7.7 ± 1.0 / 61 ± 11	-1.4 (-1.9, -0.8) / -15 (-21, -9)	6.7 ± 1.0 / 50 ± 11	7.1 ± 0.9 / 54 ± 10	-0.4 (-0.9, 0.1) / -5 (-10, 1)	7.0 ± 1.1 / 53 ± 12	7.5 ± 1.1 / 58 ± 12	-0.2 (-0.7, 0.4) / -2 (-8, 4)	7.1 ± 0.9 / 54 ± 10	7.8 ± 1.2 / 62 ± 13	-0.5 (-1.1, 0.1) / -6 (-12, 1)
BG tests/d[1]	5.6 ± 2.2	6.9 ± 2.9	-0.6 (-2.3, 1.2)	6.1 ± 2.4	6.3 ± 2.5	-0.1 (-1.1, 0.9)	6.3 ± 2.1	6.3 ± 3.0	-0.1 (-1.2, 1.1)	6.6 ± 2.2	6.2 ± 2.6	0.6 (-0.7, 2.0)
≤2 inj/≥3 inj/pump, N (%)	13/15/0 (46/54/0)	0/35/0 (0/100/0)	–	13/28/1 (31/67/2)	2/35/3 (5/88/7)	–	8/30/4 (20/71/9)	1/30/7 (3/79/18)	–	6/23/6 (17/66/17)	0/17/10 (0/63/37)	–
Insulin dose[1] (units/kg/d)	0.3 ± 0.2	0.4 ± 0.2	-0.2 (-0.3, -0.1)	0.3 ± 0.3	0.5 ± 0.3	-0.2 (-0.3, -0.1)	0.4 ± 0.3	0.6 ± 0.2	-0.2 (-0.3, -0.1)	0.5 ± 0.3	0.7 ± 0.3	-0.2 (-0.4, -0.0)
Short acting[1] (units/kg/d)	0.2 ± 0.2	0.2 ± 0.1	-0.1 (-0.2, 0.0)	0.2 ± 0.2	0.3 ± 0.2	-0.1 (-0.2, -0.0)	0.2 ± 0.2	0.3 ± 0.2	-0.1 (-0.2, -0.0)	0.3 ± 0.2	0.4 ± 0.2	-0.1 (-0.3, -0.0)
Long acting[1] (units/kg/d)	0.1 ± 0.1	0.2 ± 0.1	-0.1 (-0.1, -0.0)	0.1 ± 0.1	0.2 ± 0.1	-0.1 (-0.1, -0.0)	0.2 ± 0.1	0.3 ± 0.1	-0.1 (-0.2, -0.0)	0.2 ± 0.1	0.3 ± 0.1	-0.1 (-0.2, 0.0)
IDAA1c[1,2]	7.6 ± 1.8	9.4 ± 1.1	-1.8 (-2.9, -0.8)	7.9 ± 1.7	9.0 ± 1.5	-1.1 (-1.8, -0.3)	8.5 ± 1.7	9.7 ± 1.5	-0.8 (-1.6, 0.0)	9.1 ± 1.6	10.7 ± 1.8	-1.3 (-2.4, -0.2)

Mean ± standard deviation are shown unless specified otherwise.

Abbreviations: BG: blood glucose; HbA1c, hemoglobin A1c; IDAA1c, Insulin dose-adjusted A1c; inj: injections; Mean diff (95% CI): mean difference (95% confidence intervals); TEDDY, The Environmental Determinants of Diabetes in the Young.

[1] Missing information in some subjects.

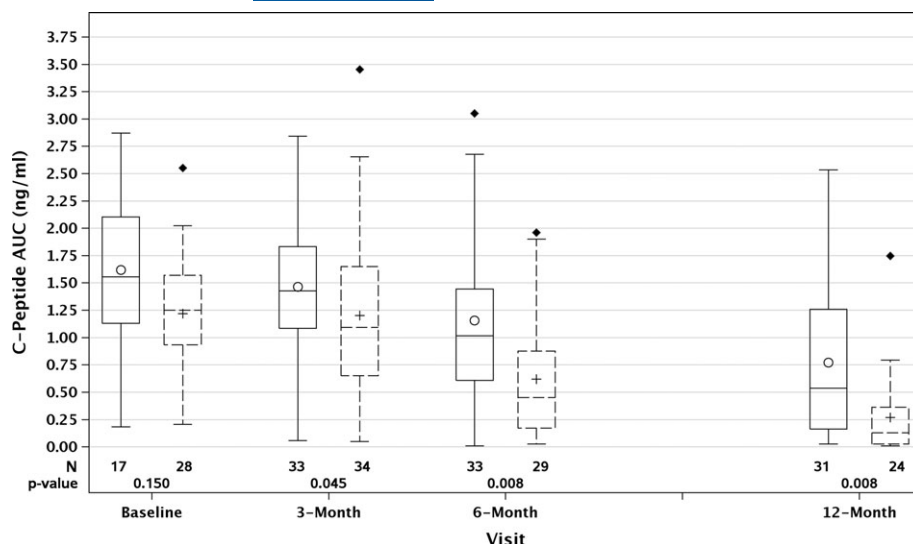[2] IDAA1c: calculated as A1c (%) + (4 × insulin dose [units/kg/d]).

FIGURE 1 Serum C-peptide area under the curve (AUC) during mixed meal tolerance test in The Environmental Determinants of Diabetes in the Young cases and community controls during the first year follow up after diagnosis of diabetes. Box plots with minimum, first quartile, median, third quartile, and maximum values. The line in the box plots indicates the median value, while the mean is denoted by "+" for cases and "○" for controls. Outliers are marked as ◆. Cases are denoted by continuous black line and controls are denoted by dotted black lines.

results did not reach statistical significance at baseline, likely because of smaller number of subjects completing MMTT at baseline. The subjects who presented with DKA at onset had peak C-peptide values at baseline between 0.25 and 1.42 ng/mL (0.08-0.47 pmol/mL) and AUC C-peptide values at baseline between 0.2 and 1.26 ng/mL (0.07-0.42 pmol/mL).

Diabetes management and other secondary outcomes are shown in Table 3. The HbA1c values tended to be lower in the TEDDY children compared with community during the first year postdiagnosis. Total insulin dose (units/kg/d) was lower throughout the first year postdiagnosis for TEDDY children, compared with community control children with similar lower patterns for both short- and long-acting insulin doses. Insulin regimen was different between the 2 groups, with TEDDY children more likely to be on ≤2 insulin injections per day and less likely to be on an insulin pump than community control children. TEDDY children had a lower IDAA1c throughout the first year postdiagnosis.

C-peptide AUC in TEDDY cases compared to community controls during the first year after diagnosis of diabetes is shown in Figure 1. TEDDY children had higher AUC C-peptide values than community controls throughout the first year postdiagnosis. However, the rates of C-peptide decline during the first year did not differ between cases and community controls (0.040 vs 0.047 per month, respectively, $P = 0.37$). In addition, the rates of C-peptide decline during the first year did not differ between cases and controls (0.041 and 0.046 per month, respectively, $P = 0.43$) after adjustment for HLA-DR3/4,DQB1*0302 and age at diagnosis.

HbA1c, insulin dose, and IDAA1c in TEDDY cases compared to community controls during the first year after diagnosis of diabetes are shown in Figure 2. TEDDY children tended to have lower HbA1c during the first year postdiagnosis (Figure 2A). While total insulin dose increased during the first year in both groups as expected, TEDDY children maintained lower insulin doses throughout the first year of follow up (Figure 2B). The IDAA1c was also lower at baseline and during the first year postdiagnosis in TEDDY children, compared with community control children (Figure 2C).

4 | DISCUSSION

While children diagnosed with type 1 diabetes through prospective monitoring studies, such as TEDDY, TrialNet, DAISY, and DiPiS, have been shown to have less DKA at the onset of diabetes,[1–3,6] it is not known if these children will have long-term benefits from early symptom-free diabetes. This is the first study to show that young general population children diagnosed with type 1 diabetes in prospective monitoring studies not only have lower HbA1c and less symptoms at diabetes onset but also have higher remaining C-peptide, lower insulin doses, and lower IDAA1c during the first year postdiagnosis compared with age-matched controls diagnosed with diabetes via community medical care.

The reported frequency of DKA at diagnosis varies widely by country from 16% to 67%, and has been shown to be inversely associated with gross domestic product, latitude, and background incidence of type 1 diabetes.[31] While the incidence has decreased in some countries to below 20%,[32] the incidence of DKA in youth (<18 years) at diagnosis in Colorado has increased from 30% to 46% between 1998 and 2012.[33] In prospective studies such as TEDDY, DKA at onset is rare, with only 8% of very young children (median age: 2.3 years) presenting in DKA.[3,6] In the TEDDY cohort overall, there has been a total of 15 children diagnosed with DKA: 8 of these children were diagnosed with diabetes below the age of 3; of the children presenting in DKA above the age of 3, 6 children did not have a TEDDY study visit within the last year before diabetes diagnosis and 1 subject was followed on a TEDDY long-distance protocol. In this study, 58% of TEDDY children (mean age 6 years) had no symptoms at diagnosis and none of them had DKA; only 14% of the community children had DKA, which is a low frequency of DKA for young general population children. TEDDY children in this study had 0% DKA, as all TEDDY children included in the JDRF follow-up study were over 3 years of age at diagnosis and had to have active follow up in TEDDY (ie TEDDY study visit during the previous 12 months before diabetes diagnosis). As this study involves multiple MMTTs during the first year postdiagnosis, it is possible that more medically committed community control families were enrolled into the study,
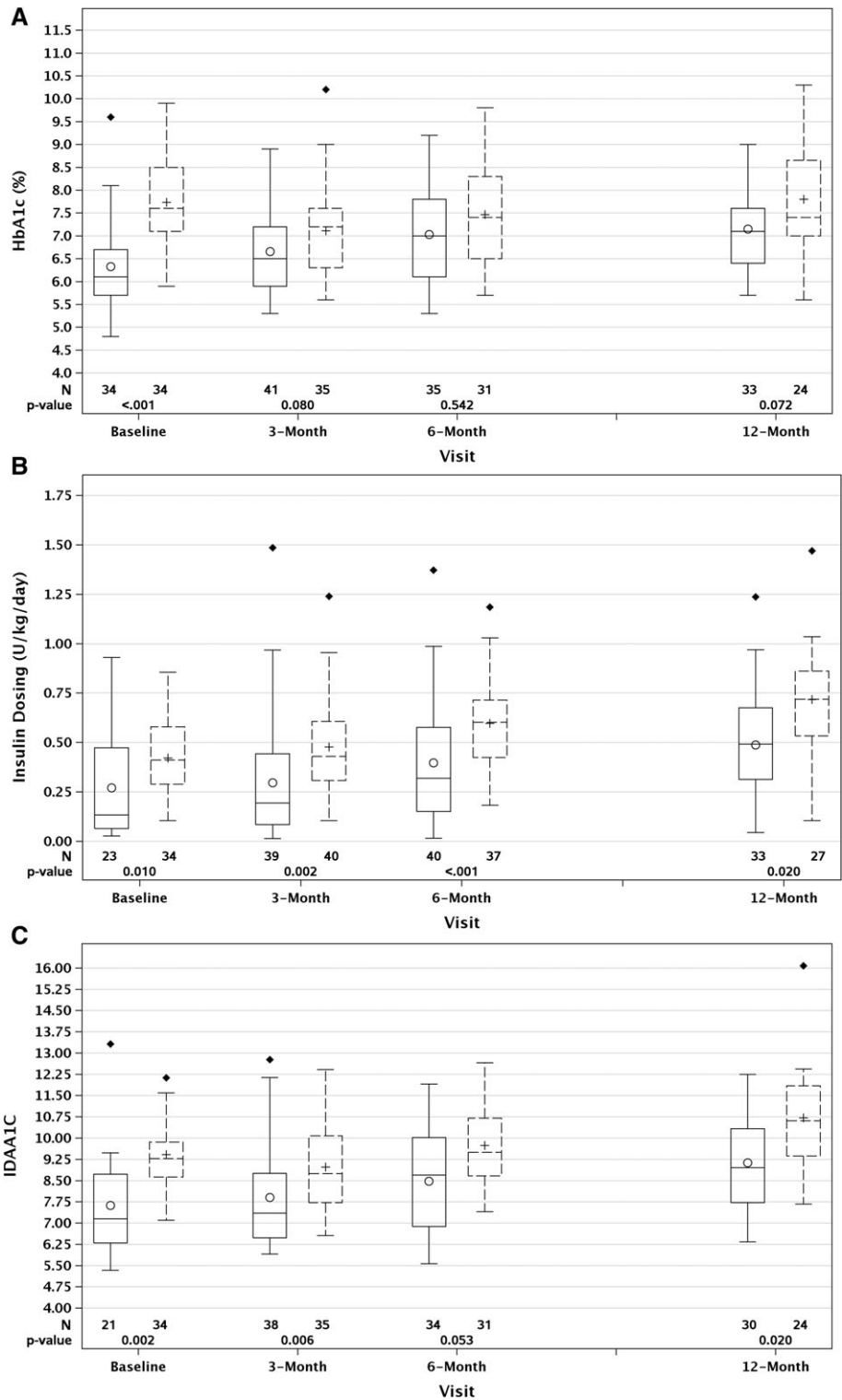
FIGURE 2 A, Hemoglobin A1c (HbA1c), B, insulin dose, and C, insulin dose-adjusted HbA1c (IDAA1c) in The Environmental Determinants of Diabetes in the Young cases and community controls during the first year follow up after diagnosis of diabetes. Box plots with minimum, first quartile, median, third quartile, and maximum values. The line in the box plots indicates the median value, while the mean is denoted by "+" for cases and "○" for controls. Outliers are marked as ◆. IDAA1c is calculated as A1c (%) + (4 × insulin dose [units/kg/d]). Cases are denoted by continuous black line and controls are denoted by dotted black lines.

or that participation in the study increased this commitment. This study included countries with both high (Finland and Sweden) and moderate (United States) incidence of type 1 diabetes and therefore represents well the influence of follow-up studies on comorbidities at diagnosis in different backgrounds.

This study appears to show a more durable improvement in endogenous islet function than seen before. A comparison of DAISY vs community subjects[22] showed lower baseline HbA1c, IDAA1c, and higher stimulated C-peptide at baseline in DAISY participants. At 6 months, C-peptide differences were no longer seen; and by 12 months, neither IDAA1c nor C-peptide was significantly different. It is important to note that the DAISY children were older at diagnosis (mean age: 12.1 years) and that a modified MMTT was used with only 1 fasting and 1 stimulated C-peptide collected at 60 minutes after a standardized liquid meal Boost High Protein. In this younger and larger cohort of TEDDY children, differences in C-peptide, insulin doses, and IDAA1c stayed significant for at least the first year postdiagnosis.

Although TEDDY children have higher C-peptide values throughout the first year postdiagnosis, the loss of C-peptide appears to be

parallel to that seen in community-diagnosed children, suggesting that TEDDY children are simply diagnosed earlier in the disease process. In an early study, rates of C-peptide decline from diabetes diagnosis were reported to be unrelated to age at diagnosis and were strikingly parallel in different age groups.[20] More recently, rates of C-peptide decline have been highly variable with most of the data derived from the placebo arm of randomized-controlled trials assessing drug interventions in newly diagnosed subjects.[16,17,21,34] Evaluation of C-peptide production after diagnosis in TrialNet showed a biphasic decline in C-peptide levels with a steeper slope of decline occurring during the first 12 months from diagnosis, then flattening between 12 and 24 months.[21] In this study, the decline in C-peptide production was much steeper in the first 6 months after diagnosis with flattening after 6 months in both the TEDDY and community children, similar to what was seen in the DAISY pilot study.[22]

Higher initial C-peptide levels in children diagnosed through prospective monitoring studies are likely to give an improved window of opportunity for type 1 diabetes intervention trials. For example, in a report on 2-year outcomes in the Protégé trial of anti-CD3 therapy, greater AUC mean C-peptide was significantly associated with a better response to drug therapy and better preservation of C-peptide over the next 2 years[35].

Limitations of this study include differences in age of onset between the 2 cohorts, in spite of the study design to match on age. As age is a known factor influencing C-peptide levels, C-peptide analyses were further adjusted by age. Although there were no selection criteria for community controls, it appears that this young group of children had a low frequency of DKA, which might result in a control group with greater residual C-peptide. If the community control group had more severe presentation at onset, the differences between the 2 groups might have been greater, as DKA at diagnosis has been associated with a lower frequency of partial remission ("honeymoon phase").[36,37]

In summary, this study shows that earlier diagnosis of type 1 diabetes in TEDDY children is associated with higher stimulated levels of residual C-peptide, lower insulin doses, and lower IDAA1c during the first year postdiagnosis, compared to controls diagnosed with diabetes through the community. These higher C-peptide levels in TEDDY children appear to represent a shift in the disease process of about 6 months. Although the loss of C-peptide appears to be parallel, ongoing follow up of these children is important to help determine whether early symptom-free diagnosis of diabetes has long-term benefits.

Conflict of interest

The authors declare that there is no conflict of interest associated with this manuscript.

Author contribution

A.K.S. designed the study, wrote manuscript, and contributed to discussion; H.E.L. contributed to discussion and reviewed/edited manuscript; X.L. researched data and reviewed/edited manuscript; R.V. contributed to discussion and reviewed/edited manuscript; J.T. reviewed/edited manuscript; W.A.H. contributed to discussion and reviewed/edited manuscript; M.J.H. reviewed/edited manuscript; S.A. contributed to discussion and reviewed/edited manuscript; B.A. contributed to discussion and reviewed/edited manuscript; A.L. contributed to discussion and reviewed/edited manuscript; M.J.R. designed the study, contributed to discussion and reviewed/edited manuscript; J.P.K. designed the study, contributed to discussion and reviewed/edited manuscript.

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