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Residual Beta Cell Function in Diabetes Children Followed and Diagnosed in the TEDDY Study compared to Community Controls

Andrea K. Steck[1], **Helena Elding Larsson**[2], **Xiang Liu**[3], **Riitta Veijola**[4], **Jorma Toppari**[5], **William A. Hagopian**[6], **Michael J. Haller**[7], **Simi Ahmed**[8], **Beena Akolkar**[9], **Åke Lernmark**[2], **Marian J. Rewers**[1], and **Jeffrey P. Krischer**[3] **the TEDDY Study Group***

[1]Barbara Davis Center for Childhood Diabetes, University of Colorado School of Medicine, Aurora, CO, USA [2]Department of Clinical Sciences, Lund University, Skåne University Hospital, Malmö, Sweden [3]Health Informatics Institute, University of South Florida, Tampa, FL, USA [4]Department of Pediatrics, PEDEGO Research Unit, MRC Oulu, Oulu University Hospital and University of Oulu, Oulu, Finland [5]Turku Department of Physiology, Institute of Biomedicine, University of Turku, and Department of Pediatrics, Turku University Hospital, Turku, Finland [6]Pacific Northwest Diabetes Research Institute, Seattle, WA, USA [7]Department of Pediatrics, University of Florida, Gainesville, FL, USA [8]Immunology of T1D, JDRF International, New York, NY, USA [9]Division of Diabetes, Endocrinology & Metabolism, National Institute of Diabetes, Digestive, & Kidney Diseases, National Institutes of Health, Bethesda, Maryland, USA

Abstract

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 HLA 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. HbA1c and Mixed Meal Tolerance Test were performed within one month of diabetes onset, then at 3, 6, and 12 months, and bi-annually thereafter.

Corresponding Author: Andrea Steck, MD, Associate Professor of Pediatrics, Barbara Davis Center for Childhood Diabetes, University of Colorado School of Medicine, 1775 Aurora Court, A140, Aurora, CO 80045-6511, USA, andrea.steck@ucdenver.edu, Phone: 303-724-6769, Fax: 303-724-6779.

*Members of the TEDDY Study Group are listed in Appendix

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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 to 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 AUC and peak C-peptide values than the community controls throughout the first year post-diagnosis. Total insulin dose and insulin dose-adjusted A1c (IDAA1c) were lower throughout the first year post-diagnosis for TEDDY compared to control children.

Conclusions—Higher C-peptide levels in TEDDY versus community-diagnosed children persist for at least 12 months following diabetes onset and seem 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

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

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 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 HbA1c and oral glucose tolerance tests (OGTT)[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 is 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 two 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 β-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 one 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 nine 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 (2.5ng/ml vs

1.6ng/ml) when compared to nine matched community children. However, those favorable patterns of IDAA1c and C-peptide were no longer apparent one year from diagnosis. Children followed before diabetes diagnosis within the DiPiS study had a lower HbA1c up to two years after diagnosis, compared to 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 one out of three 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.

METHODS

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 (01/2012–11/2015): of these 82 eligible subjects, 59 enrolled into the JDRF Follow-up study while 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, BMI, family history of diabetes, diabetes symptoms, diabetic ketoacidosis (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 versus those who did not enroll (Online Table). 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. 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 one month ofdiagnosis, then at 3, 6, and 12 months after diagnosis, and bi-annually 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.

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. 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 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.

Islet Autoantibodies

Autoantibodies to GAD65, IA-2, and ZnT8 were measured in two 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, United Kingdom. Both laboratories have previously shown high assay sensitivity and specificity, as well as concordance[28].

Statistical Analysis

Data were analyzed using the Statistical Analysis System software (version 9.4; SAS Institute, Cary, NC). For the comparison of characteristics at diagnosis of diabetes, diabetes management, and 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 since these potential confounding factors were different between TEDDY cases and community controls. Insulin-dose adjusted HbA1c (IDAA1C), an alternate measure of residual beta-cell function[30], was calculated as HbA1c (%) + [4 × insulin dose (units/kg/day)]. Two-tailed p-values less than 0.05 were considered to be statistically significant.

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

Diabetes management and other secondary outcomes are shown in Table 3. HbA1c values tended to be lower in the TEDDY children compared to community during the first year post-diagnosis. Total insulin dose (U/kg/day) was lower throughout the first year post-diagnosis for TEDDY children, compared to community control children with similar lower patterns for both short- and long-acting insulin doses. Insulin regimen was different between the two 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 insulin dose-adjusted A1c (IDAA1C) throughout the first year post-diagnosis.

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 post-diagnosis. 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 post-diagnosis (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). IDAA1c was also lower at baseline and during the first year post-diagnosis in TEDDY children, compared to community control children (Figure 2C).

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 post-diagnosis compared to 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: eight of these children were diagnosed with diabetes below the age of 3; of the children presenting in DKA above the age of 3, six children did not have a TEDDY study visit within the last year before diabetes diagnosis and one 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 (i.e. TEDDY study visit during the previous 12 months before diabetes diagnosis). As this study involves multiple MMTTs during the first year post-diagnosis, it is possible that more medically-committed community control families were enrolled into the study, or that participation in the study increased this commitment. The present study included countries with both high (Finland and Sweden) and moderate (U.S.) incidence of type 1 diabetes and therefore represents well the influence of follow-up studies on co-morbidities at diagnosis in different backgrounds.

The current study appears to show a more durable improvement in endogenous islet function than seen before. A comparison of DAISY versus 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 were 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 one fasting and one 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 post-diagnosis.

Although TEDDY children have higher C-peptide values throughout the first year post-diagnosis, the loss of C-peptide seems 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 12–24 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 two 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 seems 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

two 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 post-diagnosis, compared to controls diagnosed with diabetes through the community. These higher C-peptide levels in TEDDY children seem to represent a shift in the disease process of about 6 months. Although the loss of C-peptide seems 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

TEDDY	The Environmental Determinants of Diabetes in the Young
DAISY	Diabetes Autoimmunity Study in the Young
DiPiS	the Diabetes prediction in Skåne study
OGTT	oral glucose tolerance tests
IDAA1c	insulin dose-adjusted HbA1c
JDRF	Juvenile Diabetes Research Foundation
DKA	diabetic ketoacidosis
MMTT	Mixed Meal Tolerance Test
AUC	area under the curve
GEE	Generalized Estimating Equation

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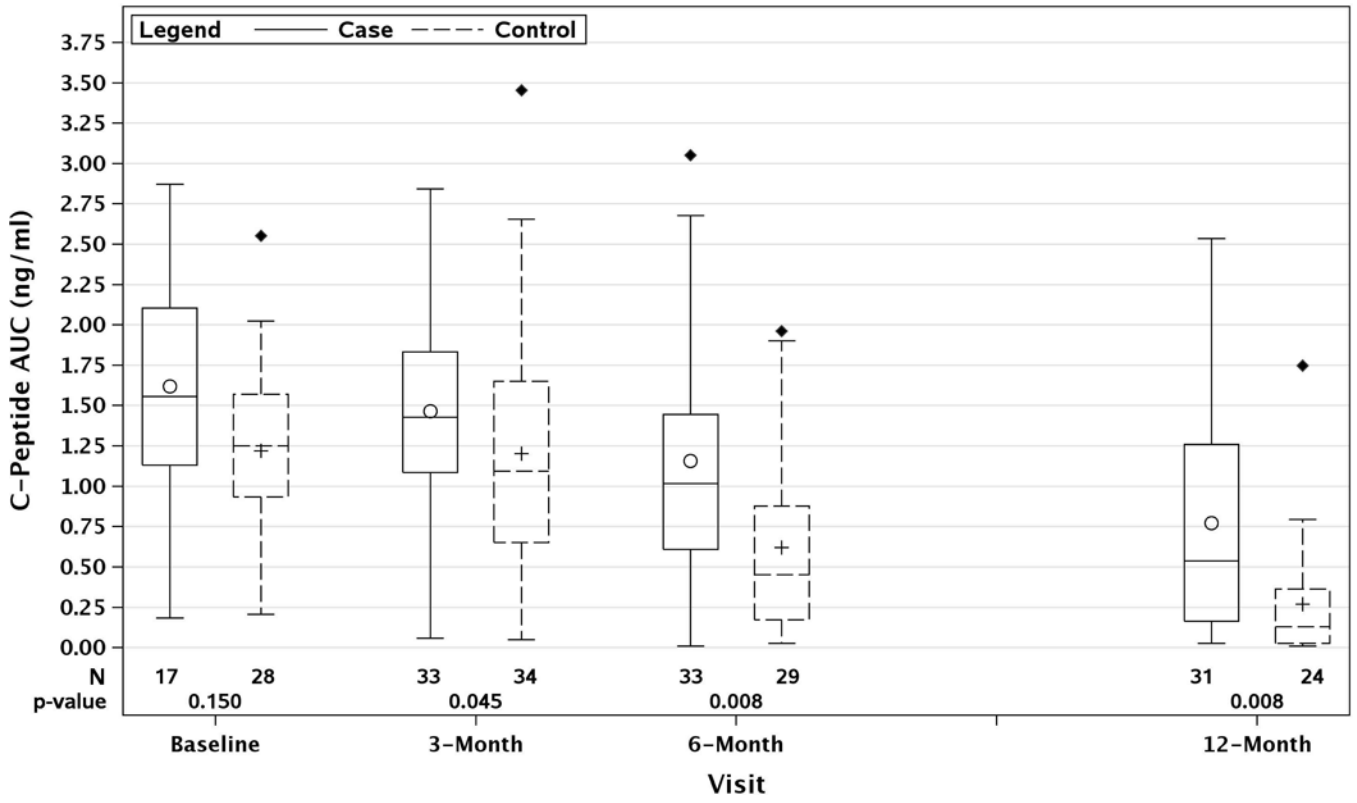
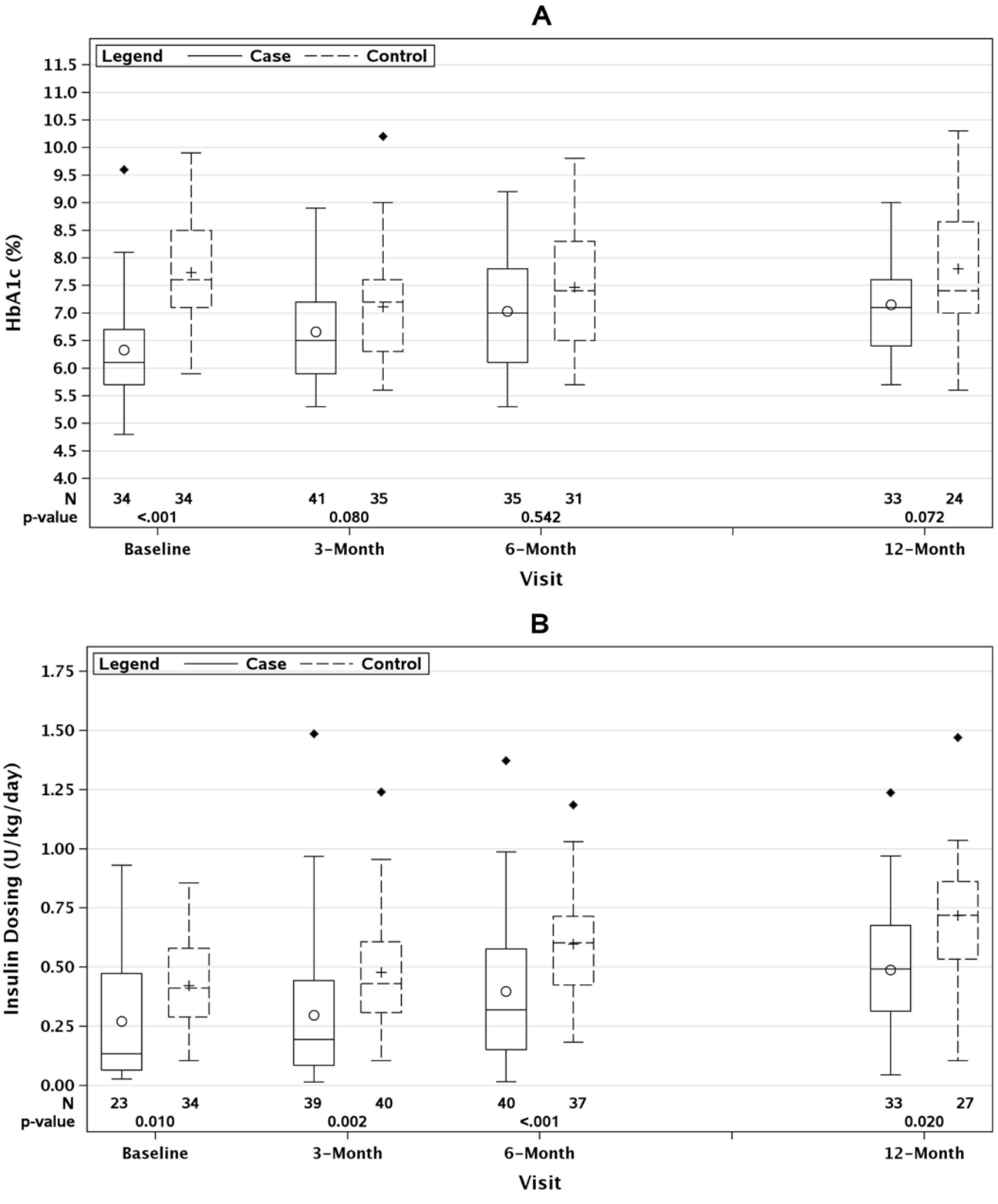


Figure 1. Serum C-peptide AUC during MMTT in TEDDY cases and community controls during the first year follow-up after diagnosis of diabetes

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 o for controls. Outliers are marked as ■.

Cases: continuous black line

Controls: dotted black lines



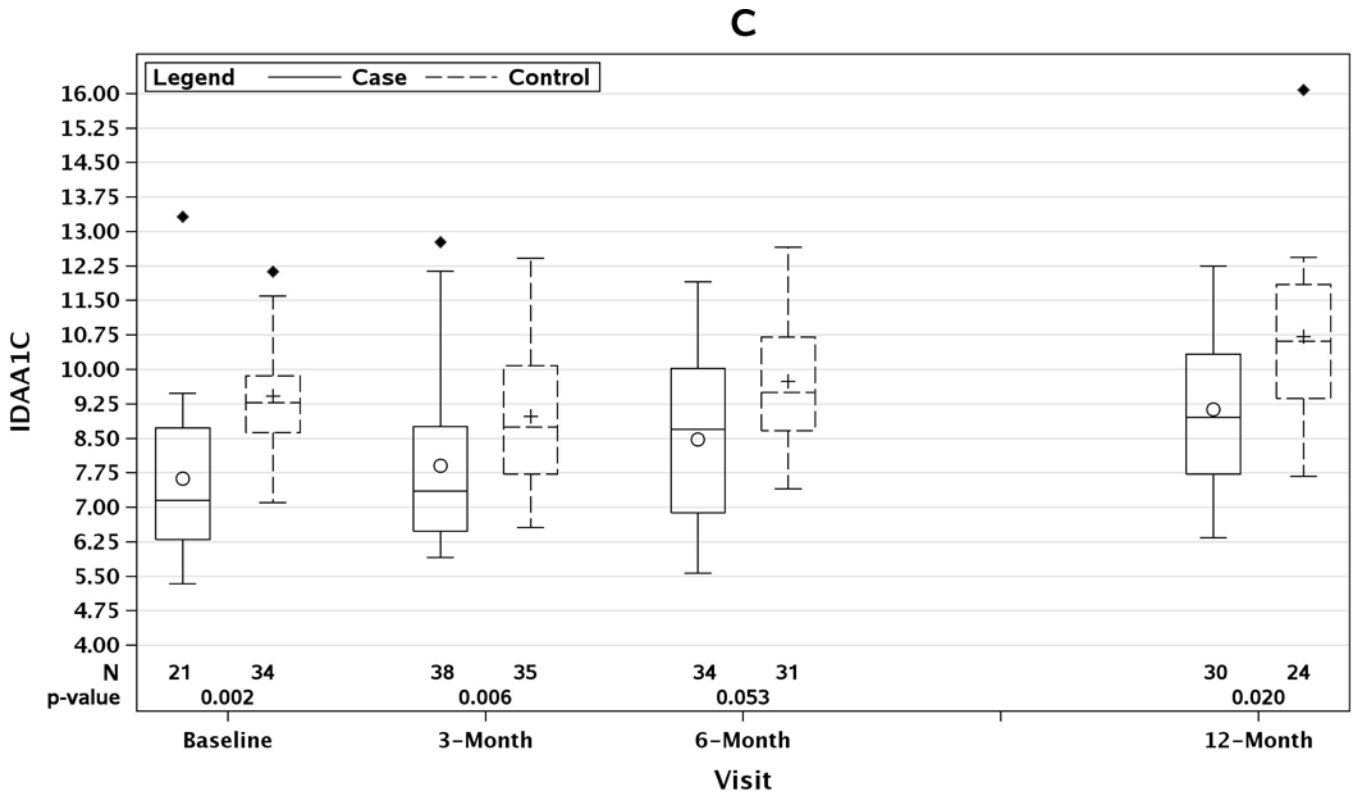


Figure 2. HbA1c (A), insulin dose (B) and IDAA1C (C) in TEDDY cases and community controls during the first year follow-up after diagnosis of diabetes

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 o for controls. Outliers are marked as ■.

IDAA1C: Insulin-dose adjusted A1c: calculated as A1c (%) + [4 × insulin dose (units/kg/day)]

Cases: continuous black line

Controls: dotted black lines

Table 1

Characteristics at diagnosis of diabetes in TEDDY cases versus community controls

	TEDDY (N=43)	Community (N=43)	P-value
Age at diagnosis (years)			0.001
Mean	6.0 ± 1.6	6.4 ± 1.8	
Range	2.8 – 10.0	3.3 – 10.5	
Gender Female, N (%)	20 (47)	27 (63)	0.21
BMI *	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 *,N (%)	24 (56)	4 (10)	0.003
# of positive autoantibodies *,†, N (%)			0.58
0	1 (4)	1 (3)	
1	5 (19)	10 (30)	
≥2	21 (78)	22 (67)	
Mean GADA level *,†	0.55 ± 0.80	0.19 ± 0.59	0.07
Mean IA-2A level *,†	1.43 ± 0.83	1.35 ± 0.85	0.39
Mean ZnT8A level *,†	0.29 ± 0.20	0.23 ± 0.18	0.81
HbA1c *, % (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

* missing information in some subjects

† autoantibody data from baseline visit

Autoantibody levels were converted to SD units away from threshold (Z scores)

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

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 month	Community (N=34) 3 month	P-value	TEDDY (N=33) 6 month	Community (N=29) 6 month	P-value	TEDDY (N=31) 12 month	Community (N=24) 12 month	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-peptideng/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

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 month	Community (N=40) 3 month	Mean Diff (95% CI) ^	TEDDY (N=42) 6 month	Community (N=38) 6 month	Mean Diff (95%CI) ^	TEDDY (N=36) 12 month	Community (N=27) 12 month	Mean Diff (95% CI) ^
HbA1c *, % (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/day *	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 *(u/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 *(u/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 *(u/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, −0.1)	0.2±0.1	0.3±0.1	−0.1 (−0.2, 0.0)
IDAA1C *,§	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

* missing information in some subjects

† BG: blood glucose

‡ inj: injections

§ IDAA1C: Insulin-dose adjusted A1c: calculated as A1c (%) + [4 × insulin dose (units/kg/day)]

^ Mean Diff (95% CI): mean difference (95% confidence intervals)