Received: 26 June 2022 | Accepted: 4 September 2022

DOI: 10.1111/pedi.13413

ISPAD International Society for Pediatric and Adolescent Diabetes | WILEY

HbA1c as a time predictive biomarker for an additional islet autoantibody and type 1 diabetes in seroconverted TEDDY children

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Funding information
Centers for Disease Control and Prevention (CDC); Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD); Juvenile Diabetes Research Foundation United States of America; National Institute of Allergy and Infectious Diseases (NIAID); NIH/NCATS Clinical and Translational Science Awards; University of Colorado, Grant/Award Number: UL1 TR002535; University of Florida, Grant/Award Number: UL1 TR000064; National Institute of Environmental Health

Abstract

Objective: Increased level of glycated hemoglobin (HbA1c) is associated with type 1 diabetes onset that in turn is preceded by one to several autoantibodies against the pancreatic islet beta cell autoantigens; insulin (IA), glutamic acid decarboxylase (GAD), islet antigen-2 (IA-2) and zinc transporter 8 (ZnT8). The risk for type 1 diabetes diagnosis increases by autoantibody number. Biomarkers predicting the development of a second or a subsequent autoantibody and type 1 diabetes are needed to predict disease stages and improve secondary prevention trials. This study aimed to investigate whether HbA1c possibly predicts the progression from first to a subsequent autoantibody or type 1 diabetes in healthy children participating in the Environmental Determinants of Diabetes in the Young (TEDDY) study.

Research Design and Methods: A joint model was designed to assess the association of longitudinal HbA1c levels with the development of first (insulin or GAD autoantibodies) to

Sciences (NIEHS); National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), Grant/Award Numbers: HHSN267200700014C, U01 DK128847, U01 DK124166, UC4 DK117483, UC4 DK112243, UC4 DK106955, UC4 DK100238, UC4 DK95300, UC4 DK63836, UC4 DK63863, UC4 DK63865, UC4 DK63821, UC4 DK63861, UC4 DK63829, U01 DK63790, U01 DK63836, U01 DK63863, U01 DK63865, U01 DK63821, U01 DK63861, U01 DK63829

a second, second to third, third to fourth autoantibody or type 1 diabetes in healthy children prospectively followed from birth until 15 years of age.

Results: It was found that increased levels of HbA1c were associated with a higher risk of type 1 diabetes (HR 1.82, 95% CI [1.57–2.10], $p < 0.001$) regardless of first appearing autoantibody, autoantibody number or type. A decrease in HbA1c levels was associated with the development of IA-2A as a second autoantibody following GADA (HR 0.85, 95% CI [0.75, 0.97], $p = 0.017$) and a fourth autoantibody following GADA, IAA and ZnT8A (HR 0.90, 95% CI [0.82, 0.99], $p = 0.036$). HbA1c trajectory analyses showed a significant increase of HbA1c over time ($p < 0.001$) and that the increase is more rapid as the number of autoantibodies increased from one to three ($p < 0.001$).

Conclusion: In conclusion, increased HbA1c is a reliable time predictive marker for type 1 diabetes onset. The increased rate of increase of HbA1c from first to third autoantibody and the decrease in HbA1c predicting the development of IA-2A are novel findings proving the link between HbA1c and the appearance of autoantibodies.

KEYWORDS

children, GADA, HbA1c, IA-2A, IAA, islet autoantibodies, type 1 diabetes, ZnT8A

1 | INTRODUCTION

Autoimmune type 1 diabetes (type 1 diabetes) is preceded by autoantibodies targeting islet beta cell autoantigens. The autoantibodies against glutamic acid decarboxylase (GADA), insulin (IAA), islet antigen-2 (IA-2A), and zinc transporter 8 (ZnT8A), in turn serve as the strongest predictors of type 1 diabetes clinical onset to date. The development of one or several islet beta cell autoantibodies is a hallmark of an ongoing autoimmune process conferring an increased risk of type 1 diabetes. It has been estimated that children with multiple beta cell autoantibodies have a 70% risk to develop type 1 diabetes in 10 years and a lifetime risk approaching 100%.[1] Specific HLA-DR-DQ genotypes together with unknown exogenous factors are likely to trigger an autoimmune reaction against the beta cell autoantigens, predominantly GAD or insulin reflected by the first appearing autoantibody. In recent years, HLA associated endotypes have been identified, the first one is the predisposition of HLA-DR4-DQ8 haplotype associated with IAA as the first appearing autoantibody and the second is the predisposition of HLA-DR3-DQ2 associated with GADA as the first appearing autoantibody.[2] Furthermore, three distinct stages of type 1 diabetes have been proposed to characterize disease progression starting with two or more autoantibodies and normoglycemia (stage 1), followed by dysglycaemia (stage 2), and lastly clinical onset of type 1 diabetes with hyperglycemia and symptoms as defined by ADA and WHO (stage 3).[3] However, the time between these stages varies from weeks to years and complicates the prediction of disease progression and the design of secondary prevention trials. Additional biomarkers to complement autoantibody analysis are therefore greatly warranted to predict time to an additional autoantibody or to type 1 diabetes clinical onset. The development of accurate time prediction tools would improve therapeutic interventions aiming to maintain beta cell function. Increase of the glycated hemoglobin A1c (HbA1c), the well-known dysglycaemia marker, has been evaluated in several studies as a biomarker for type 1 diabetes progression and suggested to be used as a tool for time to diagnosis prediction in children at increased risk.[4–6] The Environmental Determinants of Diabetes in the Young (TEDDY) study is a multi-site, multi-country (Finland, Germany, Sweden, and United States) prospective study aimed to study environmental factors triggering islet autoimmunity and to explore the progression of type 1 diabetes by following children at increased genetic risk for type 1 diabetes from birth until 15 years of age.[7] The aim of the present study was to investigate the possible association between HbA1c and the progression to an additional autoantibody or to the diagnosis of type 1 diabetes in seroconverted TEDDY children during follow-up and if so to investigate whether there is a difference between the two endotypes of IAA or GADA as the first appearing autoantibody.

2 | MATERIALS AND METHODS

TEDDY is a prospective cohort study conducted in three clinical research centers in Europe (Finland, Germany, and Sweden) and three in the United States (Colorado, Georgia/Florida, and Washington State) aiming primarily to identify environmental triggers of autoimmunity and progression to type 1 diabetes. The study design, eligibility, and methods were previously reported.[8] A total of 424,788 newborns were screened for high-risk HLA-DR-DQ genotypes associated with type 1 diabetes at the different TEDDY sites between September 2004 and February 2010. The eligible 8556 children with

TABLE 1 Islet autoantibody combinations in the four subcohorts observed in this study

Subcohorts	Autoantibody transition state, or type 1 diabetes onset	Possible subsequent autoantibodies
IAA (1st autoantibody)	1st to 2nd or type 1 diabetes	GADA IA-2A ZnT8A >1 autoantibody[a]
GADA (1st autoantibody)	1st to 2nd or type 1 diabetes	IAA IA-2A ZnT8A >1 autoantibody[b]
IAA + GADA	2nd to 3rd or type 1 diabetes	IA-2A ZnT8A IA-2A + ZnT8A
IAA + GADA + ZnT8A	3rd to 4th or type 1 diabetes	IA-2A

[a]>1 autoantibodies; refers to any combination of GADA, IA-2A, or ZnT8A islet autoantibodies becoming positive at the same time.
[b]>1 autoantibody; refers to any combination of IAA, IA-2A, or ZnT8A islet autoantibodies becoming positive at the same time.

consents were enrolled and 89% represented the general population while the remaining 11% had a first-degree relative with type 1 diabetes. Enrolled healthy children started the prospective clinical follow-up from 3 months of age and were monitored for development of islet autoantibodies every 3 month during the first 4 years and semiannually until 15 years of age. Once seroconverted, children with one or several islet autoantibodies continued the study follow-up each third month until 15 years of age or until they developed type 1 diabetes.

2.1 | Study participants

The study participants included were all enrolled TEDDY children who reported a persistent confirmed positivity for islet autoantibody as of May 31, 2021. These subjects were divided into four subcohorts depending on their islet autoantibody combination (IAA, GADA, IA-2A, and ZnT8A) of the first, second, third, or fourth appearing islet autoantibody. The progression from the first autoantibody to the second or type 1 diabetes, the second to the third or type 1 diabetes, and the third to the fourth or type 1 diabetes are referred to as transition states in this study. The given starting state islet autoantibody combination at first visit with positivity for the respective autoantibodies in each subcohort is presented in Table 1, together with the possible types of islet autoantibodies that could subsequently appear.

2.2 | HLA analysis

Cord-blood or heel stick capillary blood samples taken in the first months of life were used to identify high risk HLA DR-DQ genotypes meeting the eligibility criteria of the TEDDY protocol. Typing utilized PCR amplification, Sanger sequencing, oligonucleotide probe hybridization, and/or denaturing gel electrophoresis.[9] The HLA genotypes were then confirmed at 9–12 months of age using reverse line blot hybridization at a central HLA Reference Laboratory at Roche Molecular Systems, Oakland, CA.[10]

2.3 | Islet autoantibody analysis

Islet autoantibody surveillance for IAA, GADA, and IA-2A started at 3–4 months of age. It was then repeated every third month until 4 years of age, and thereafter every 3–6 months until 15 years of age. In order to confirm the islet autoantibody positivity, IAA, GADA, and IA-2A were analyzed in two different reference laboratories, one in the United States at Barbara Davis Center for Childhood Diabetes at the University of Colorado Denver and the other in Europe at the University of Bristol in the United Kingdom, by radiobinding assays as previously described.[11–13] Both reference laboratories have high sensitivity and high specificity as well as concordance for the islet autoantibody assays. A detected autoantibody was considered as persistent when confirmed by both reference laboratories in a sample drawn at a consecutive follow-up study visit. Persistent autoimmunity was defined by the presence of one or several persistent confirmed autoantibodies. The ZnT8A surveillance started once a child was positive but not confirmed for another primary islet autoantibody (IAA, GADA, IA-2A). ZnT8A were also analyzed at one of the two reference laboratories and considered persistent upon two consecutive positive samples in one of the reference labs.[14]

2.4 | HbA1c test

The HbA1c test was performed from the 9 months TEDDY visit in islet autoantibody positive children and every third month thereafter until 15 years of age. This requirement for HbA1c measurement was added to the TEDDY protocol 4 years after the start of the study. HbA1c samples were analyzed using an ion-exchange HPLC method on a Tosoh G8 instrument at the Diabetes Diagnostic Laboratory (DDL) at the University of Missouri, standardized using the Diabetes Control and Complications Trial reference method (imprecision coefficient of variation <1.3%).[15,16]

2.5 | Statistical analysis

The association between HbA1c and the transition from one islet beta cell autoantibody state to the subsequent autoantibody transition state was assessed using joint models of competing risk and longitudinal data. The joint models defined time as the time in years from the start of the initial state. The competing risks models studied the relationships between the covariates and the risks of transitioning from a given autoantibody state to the next autoantibody state or type 1 diabetes diagnosis. Four separate sets corresponding to the four

TABLE 2 Demographics, number of HbA1c measurements and number of type 1 diabetes diagnosis for next autoantibody state are presented for the subjects in the four subcohorts

Subcohorts Autoantibody	IAA first $n = 300$	GADA first $n = 361$	IAA + GADA $n = 257$	IAA + GADA + ZnT8A $n = 115$
Country, *n* (%)				
United States	98 (33)	133 (37)	80 (31)	43 (38)
Finland	95 (32)	71 (20)	65 (25)	33 (29)
Germany	18 (6)	19 (5)	25 (10)	5 (4)
Sweden	89 (30)	138 (38)	87 (34)	34 (30)
Gender, *n* (%)				
Female	139 (46)	168 (47)	116 (45)	54 (47)
Male	161 (54)	193 (53)	141 (55)	61 (53)
First degree relative, *n* (%)				
Yes	66 (22)	62 (17)	57 (22)	23 (20)
No	234 (78)	299 (83)	200 (78)	92 (80)
HLA genotype, *n* (%)				
DR4/DR3	144 (48)	177 (49)	161 (63)	66 (57)
DR4/DR4	54 (18)	56 (16)	39 (15)	20 (17)
DR4/DR8	62 (21)	43 (12)	28 (11)	14 (12)
DR3/DR3	26 (9)	79 (22)	15 (6)	8 (7)
Other	14 (5)	6 (2)	14 (5)	7 (6)
Baseline Age, median (min-max)	2.0 (0.3–13.7)	5.0 (0.3–14.0)	2.8 (0.5–14.6)	5.2 (1.2–13.8)
Number HbA1c[a], median (min-max)	9 (1–43)	8 (1–34)	3 (1–40)	5 (1–43)
Number of type 1 diabetes[b]	14	11	28	15

Note: Single autoantibody positive (IAA first and GADA first) at first autoantibody positive visit. IAA + GADA at first visit with two positive autoantibodies. IAA + GADA + ZnT8A at first visit with three autoantibodies.

[a]Number of HbA1c measures until next state.

[b]Number of type 1 diabetes diagnoses for next state.

different starting states, IAA first, GADA first, IAA + GADA, and IAA + GADA + ZnT8A were analyzed. The corresponding subcohorts were defined as the subjects going through the four starting states under consideration. HLA (DR3/DR4 yes or no), gender, country, BMI-z score, and HbA1c were included as covariates in the competing risks model and proportional hazards for competing events are assumed. Longitudinal models are used to model the change of HbA1c and BMI-z scores over time. The trajectories of HbA1c and BMI-z scores were modeled by longitudinal mixed effects models with constant, linear, and quadratic orthogonal polynomials. All HbA1c data from the initial autoantibody visit were included and HbA1c data after the time of type 1 diabetes diagnosis were excluded. Due to the multiplicity of subcohorts and events, a consecutive $p < 0.01$ was considered statistically significant. Technical details of the statistical models are described in the supplemented Technical Appendix (Figure 1A–D).

3 | RESULTS

Demographics, number of HbA1c measures and number of type 1 diabetes diagnoses for the next autoantibody state, for the four subcohorts at the first visit with a single autoantibody (IAA first and GADA first), the first visit with two autoantibodies (IAA and GADA), and the first visit with three autoantibodies (IAA, GADA, and ZnT8A) are presented in Table 2. The number of subjects in each of the four subcohorts at the first visit with the given starting state autoantibody was 300 IAA first appearing, 361 GADA first appearing, 257 IAA and GADA double positive, and 115 IAA, GADA and ZnT8A triple positive. The subcohorts are not mutually exclusive, thus one child could be included in one or several subcohorts, for example if the child transitioned from the one autoantibody subcohort to the two autoantibody subcohort by developing an additional autoantibody.

Complete results from the joint model analyses for all four subcohorts with all proportional hazard ratios of covariates (HLA (DR3/DR4 yes or no), gender, country, BMI-z score, and HbA1c) for each of the autoantibody transition states or type 1 diabetes (referred as events) are presented in Table S1A–D and presented below for each of the four subcohorts. The joint model analysis results yield estimated HbA1c trajectory curves for every subject in each event type within each subcohort. These results are visualized by plotting the mean estimated HbA1c for every subject in each event within each subcohort, in retrospective landmark plots going back 5 years in time from each event or transition into a subsequent islet beta cell autoantibody (Figure 1A–D).

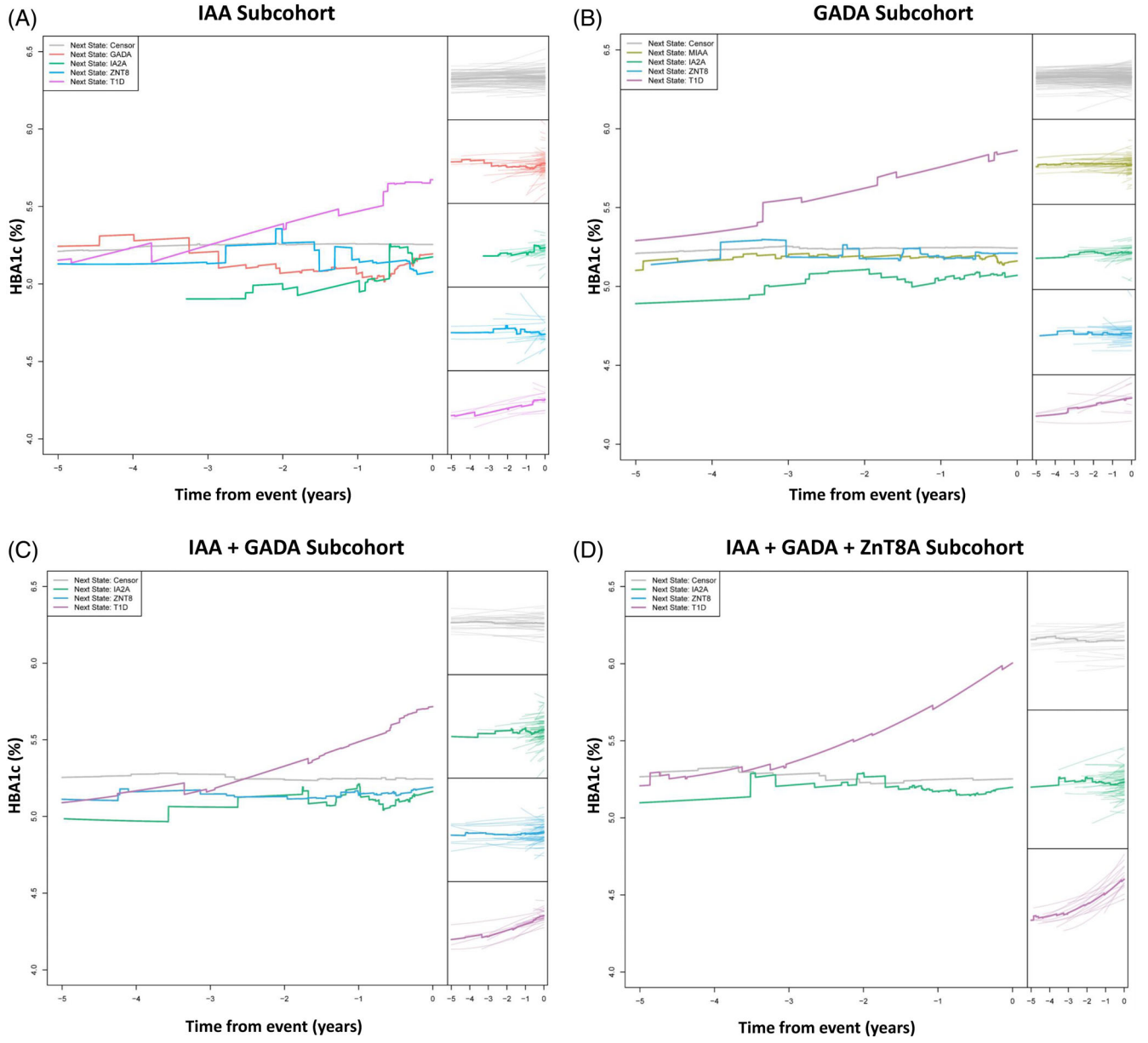

FIGURE 1 Retrospective landmark plots of HbA1c going back 5 years from each event. The left-hand panels show mean curves, and the right-hand panel shows individual curves for each event. The diagrams present each subcohort: (A) IAA single autoantibody positives; (B) GADA single autoantibody positives; (C) IAA as well as GADA positives; and (D) IAA, GADA together with ZnT8A positives. The left panels present mean curves of HbA1c going 5 years back in time, and the right panel presents individual subject curves for each event. The development of type 1 diabetes is associated with increased HbA1c in all four subcohorts. The slope of the increase also increases from one to two to three autoantibodies. Multiple autoantibody events are excluded from these Landmark plots. Censored gray lines present subjects that have lost follow-up before the transition into the next event of autoantibody development or type 1 diabetes.

3.1 | IAA single islet autoantibody subcohort and the transition to the next event (GADA, IA-2A, ZnT8A, >1 autoantibodies, or type 1 diabetes)

Increased levels of HbA1c were associated with a higher risk of developing type 1 diabetes (HR 1.27, 95% CI [1.16, 1.39], $p < 0.001$). The landmark plot shows the increase of HbA1c in IAA positive children from 5 years back from type 1 diabetes onset (Figure 1A). No statistically significant association between HbA1c and the transition from IAA as the single autoantibody to any subsequent second autoantibody (GADA, IA-2A, or ZnT8A) or multiple subsequent autoantibodies was found (Table S1A). In IAA positive children, HLA DR3/DR4 heterozygosity was associated with GADA as the second autoantibody (HR 1.89, 95% CI [1.27, 2.800], $p = 0.002$). Being an FDR with IAA was associated with two or more autoantibodies (HR 3.707, 95% CI [1.754, 7.834], $p < 0.001$). The HbA1c trajectory analysis in this subcohort showed a roughly linear increase of HbA1c over time (estimated covariate 0.34 *SE* 0.06, $p < 0.001$).

3.2 | GADA single islet autoantibody subcohort and the transition to the next event (IAA, IA-2A, ZnT8A, >1 autoantibodies, or type 1 diabetes)

Comparable to the IAA only subcohort, increased HbA1c was only significantly associated with type 1 diabetes as the subsequent transition event after GADA as a single autoantibody (HR 1.82, 95% CI [1.59, 2.07], $p < 0.001$). The landmark plot (Figure 1B) illustrates the linear increase of HbA1c during the 5 years prior to the type 1 diabetes event in GADA only positive children. HbA1c was not associated with the risk of any second islet autoantibody in GADA only positive children. However, lower HbA1c levels were significantly associated with IA-2A (HR 0.85, 95% CI [0.75, 0.97], $p = 0.017$) as a second autoantibody following GADA (Table S1B). HLA DR3/DR4 heterozygosity was associated with IAA as the second autoantibody following GADA as the first (HR 2.16, 95% CI [1.43, 3.26], $p = 0.001$). The trajectory analysis of HbA1c present also for this GADA only subcohort a roughly linear increase of HbA1c over time (estimated covariate 0.64, *SE* 0.05, $p < 0.001$).

3.3 | IAA + GADA subcohort and the transition to the next event (ZnT8A, IA-2A, ZnT8A + IA-2A, or type 1 diabetes)

Increased HbA1c levels were associated with type 1 diabetes (HR 1.82, 95% CI [1.58,2.10], $p < 0.001$) in children positive for both IAA and GADA. The linear increase of HbA1c 5 years before type 1 diabetes clinical onset is presented in the landmark plot in Figure 1C. Increased HbA1c was not associated with any third autoantibody (Table S1C). Similar to the two previously mentioned single autoantibody subcohorts, trajectories of HbA1c increased over time (estimated covariate 0.65, *SE* [0.06], $p < 0.001$) in this subcohort of children with two autoantibodies. Female gender was associated with IA-2A as the third autoantibody preceded by GADA and IAA (HR 1.81, 95% CI [1.17, 2.79], $p = 0.007$).

3.4 | IAA, GADA, and ZnT8A subcohort and the transition to the next event (IA-2A or type 1 diabetes)

In this subcohort with three autoantibodies, increased HbA1c levels were associated with type 1 diabetes clinical onset (HR 2.12, [1.79, 2.51], $p < 0.001$). The increase of HbA1c was linear (slope estimate 1.37, *SE* [0.148], $p < 0.001$) with increasing rate (quadratic estimate 0.47, *SE* [0.092], $p < 0.001$) over time as proximity to clinical onset of type 1 diabetes increases. The increased trajectories of HbA1c 5 years back from the development of type 1 diabetes in the subgroup with three autoantibodies is illustrated in Figure 1D. IA-2A as the fourth autoantibody was not associated with higher levels of HbA1c, but possibly suggested lower HbA1c levels (HR 0.90, 95% CI [0.82, 0.99], $p = 0.036$) (Table S1D).

4 | CONCLUSIONS

The main result of this study is the association of increasing HbA1c levels over time with significantly higher hazard ratios for type 1 diabetes, indicating a higher risk for the type 1 diabetes event, regardless of prior islet beta cell autoantibody number or combination. There was no association between increasing HbA1c and the transition to positivity for the second, third, or fourth islet beta cell autoantibody. However, the HbA1c trajectory analysis revealed a linear increase of HbA1c, in progression to type 1 diabetes, irrespective of the number and combinations of autoantibodies, larger HbA1c rate of increase with increasing autoantibody number from one to three autoantibodies, and finally increasing rate of HbA1c over time as proximity to type 1 diabetes diagnosis increases. The landmark plots presented a rise of HbA1c starting as early as 5 years prior to type 1 diabetes clinical onset. Nevertheless, the autoantibody transition from GADA or IAA, GADA and ZnT8A to IA-2A as the second or fourth autoantibody associated with lower levels of HbA1c is a novel finding emphasizing further investigation of autoantibodies and HbA1c together as biomarkers in the prediction of type 1 diabetes. To our knowledge, this is the first study evaluating the association between HbA1c and the progression to an additional autoantibody of specific combination in general population children who carried increased HLA-conferred risk of type 1 diabetes, had seroconverted positive for at least one islet autoantibody and were younger than 15 years of age.

The autoantibody positive TEDDY cohort represents the strength of this study with a relatively large number of autoantibody positive children from the general population, followed from birth until 15 years of age in an accurate islet beta cell autoantibody surveillance program for various numbers and combinations of islet beta cell autoantibodies. The heterogeneity in the TEDDY cohort and the relatively large number of autoantibody positive children made it possible to distribute the children in different subcohorts with different combinations and numbers of autoantibodies.

The benefit of the statistical joint model used in this study that combined longitudinal and survival models is that the estimates of factors such as HbA1c were comparable across the different autoantibody categories since the underlying hazard function was the same.[17]

One limitation of this study was the inability to analyze all combinations of islet beta cell autoantibodies (IA-2A first and ZnT8A first or both without any of IAA or GADA) due to limited number of children or progression to type 1 diabetes diagnosis in less than 3 months. Another limitation was the HbA1c not analyzed in TEDDY until 4 years after the study had started, therefore some children had limited HbA1c information.

Consistent with our results, it was reported in the population-based prospective Finnish Diabetes Prediction and Prevention (DIPP) study that a 10% increase of HbA1c during 3–12 months in children with multiple islet autoantibodies predicted type 1 diabetes diagnosis after a median time of 1.1 years. Moreover, mean HbA1c levels remained stable in autoantibody positive children who did not progress to type 1 diabetes.[4] Similar results were recently reported in an international study showing that an increase of HbA1c of 20%–30% from a previous sample predicted type 1 diabetes onset and appearance of first autoantibody but not any multiple autoantibodies.[18] Our study adds to these two findings by evaluating whether increased

HbA1c is associated with a specific autoantibody type or combination as well as the risk of developing a subsequent autoantibody or type 1 diabetes in seroconverted children with high HLA risk.

The disease pathway to type 1 diabetes is heterogenous and associated with many factors including HLA genotype, age, age at the first appearing islet autoantibody, type of first appearing autoantibody, gender, and BMI giving rise to different endotypes.[2,19] Considering this, the TEDDY cohort was analyzed in two subcohorts with IAA or GADA as the first appearing autoantibody. The present analysis showed, however, that lower levels of HbA1c in GADA single positive TEDDY children was associated with the risk to develop IA-2A as the second autoantibody.

Irrespective of blood glucose levels reflecting beta cell function, a decrease in hemoglobin or iron can increase the HbA1c level.[20–22] The HbA1c trajectories in the current study show an increase in HbA1c over time in autoantibody positive children driven by those who progress to type 1 diabetes. This HbA1c increase is still within normoglycemic ranges detected up to years before onset. We have previously shown in autoantibody positive TEDDY children an inverse association of mean corpuscular hemoglobin (MCH) and mean corpuscular volume (MCV) with HbA1c,[23] indicating a decrease in iron levels generally caused by an aberrant erythropoiesis or a reduction in iron intake or absorption.[24,25] Thus, further research is required to clarify whether there are common factors associated with erythropoiesis and development of type 1 diabetes.

Unexpectedly, increased risk for developing IA-2A in GADA positive children and those with IAA, GADA, and ZnT8A was associated with lower levels of HbA1c. This may be explained by a more aggressive autoimmune attack on the beta cells leading to autoantibody spreading or insulin leakage into the bloodstream, as IA-2A positivity is known to confer a rapid progression risk of type 1 diabetes.[14,26,27]

Type 1 diabetes disease process is extremely heterogenous and varies with age, genetics, BMI, and sex.[2,28] The prediction of disease progression in pre-symptomatic type 1 diabetes children at stage 1 or 2 is currently made by autoantibody surveillance programs together with regular OGTTs and HbA1c monitoring. Within these follow-up programs, diabetic ketoacidosis can effectively be prevented, but close follow-up is costly and limits public health implementation.[29,30] However, biomarkers predicting the progression from one stage of type 1 diabetes to the next are limited, and more accurate predictive biomarkers are needed to complement the autoantibody screening. Given that the risk of multiple autoantibodies is age-related and declines exponentially by age,[31] there is a need for additional studies evaluating age-related biomarkers. An ability to predict time more accurately to type 1 diabetes progression would improve clinical trial designs and move us closer towards personalized medicine. This study shows the high impact of HbA1c as a time predictive biomarker for type 1 diabetes onset. Thus, the joint model analysis designed in this study could be further developed with HbA1c as a tool predicting time to type 1 diabetes diagnosis.

In conclusion, rising HbA1c reflects deteriorating beta cell function several years before clinical onset of type 1 diabetes. While HbA1c increase was not associated with the development of a subsequent additional autoantibody, the association between increased HbA1c over time and the development of type 1 diabetes makes HbA1c a useful time predictive marker for type 1 diabetes onset. Lower levels of HbA1c associated with IA-2A as a second autoantibody following GADA or as the fourth autoantibody following GADA, IAA, and ZnT8A need further investigation.

AUTHOR CONTRIBUTIONS

Falastin Salami proposed the analysis, interpreted the findings, wrote, and edited the manuscript. Roy Tamura and Lu You designed the statistical model, performed the statistical analysis, reviewed, and edited the manuscript. Carina Törn proposed the analyses, reviewed, and edited the manuscript. Helena Elding Larsson, Markus Lundgren, Riitta Veijola, Michael J. Haller, reviewed and edited the manuscript. Åke Lernmark, Jeffrey Krischer, Anette-Gabriele Ziegler, Jorma Toppari, Marian Rewers, J.-X. S., William Hagopian, Beena Akolkar, designed the study and reviewed and edited the manuscript. Åke Lernmark is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

ACKNOWLEDGMENTS

A special thanks to all the TEDDY children and their families from each of the six sites in Europe and the United States for participating in the TEDDY study. We also thank all TEDDY co-workers for all their efforts and the tremendous international teamwork.

FUNDING INFORMATION

The TEDDY Study is funded by U01 DK63829, U01 DK63861, U01 DK63821, U01 DK63865, U01 DK63863, U01 DK63836, U01 DK63790, UC4 DK63829, UC4 DK63861, UC4 DK63821, UC4 DK63865, UC4 DK63863, UC4 DK63836, UC4 DK95300, UC4 DK100238, UC4 DK106955, UC4 DK112243, UC4 DK117483, U01 DK124166, U01 DK128847, and Contract No. HHSN267200700014C from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute of Allergy and Infectious Diseases (NIAID), Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), National Institute of Environmental Health Sciences (NIEHS), Centers for Disease Control and Prevention (CDC), and JDRF. This work is supported in part by the NIH/NCATS Clinical and Translational Science Awards to the University of Florida (UL1 TR000064) and the University of Colorado (UL1 TR002535). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The generated and analyzed data presented in this study will be made available in the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Central Repository at https://www.niddkrepository.org/studies/teddy.

ETHICS STATEMENT

The study was approved by local regional ethics boards in each of the participating countries and was also monitored by an external committee established by the National Institute of Health (NIH).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Salami F, Tamura R, You L, et al. HbA1c as a time predictive biomarker for an additional islet autoantibody and type 1 diabetes in seroconverted TEDDY children. *Pediatr Diabetes*. 2022;23(8):1586-1593. doi:10.1111/pedi.13413