Personalizing Early-Stage Type 1 Diabetes in Children

Catarina Limbert,[1,2] *Thekla von dem Berge,*[3] *and Thomas Danne*[3,4]

Diabetes Care 2023;46:1747–1749 | https://doi.org/10.2337/dci23-0025

Two recent trials report positive results of disease-modifying therapies suggesting an opportunity to delay type 1 diabetes (T1D) with teplizumab or preserve residual β-cell function with oral verapamil and possibly even reduce its associated morbidity, mortality, and overall burden, for individuals and society (1–3). In the recent U.S. Food and Drug Administration approval of teplizumab for treatment of early-stage T1D from age 8 years, a change can be seen in the paradigm from insulin substitution to disease modification. As a consequence, this raises the issue of general population screening for asymptomatic T1D 100 years after the first clinical use of insulin. Islet autoantibodies (antibodies against insulin, GAD [GAD65], tyrosine phosphatase antigen-2 [IA-2], and zinc transporter 8 [ZnT8]) are detected in the blood prior to the development of clinical disease in 95% of patients (3). More than 80% of individuals prone to develop T1D show signs of autoimmunity, reflected by circulating autoantibodies already at preschool age, long before the onset of hyperglycemia (3). Based on these insights, a new definition of T1D has been proposed and is being widely adopted, in which the preclinical phase is viewed as part of the disease and identified as having distinct stages. Stage 1 includes people with multiple autoantibodies but normoglycemia (4), stage 2 includes people with multiple autoantibodies and dysglycemia (defined at present with use of oral glucose tolerance testing), and people at stage 3 have clinical T1D. Stages 1 and 2 are referred to as "early-stage" T1D. There is international consensus that the presence of two or more islet autoantibodies is the early presymptomatic stage of T1D, and regulatory bodies have given a positive opinion on use of two or more islet autoantibodies as biomarkers for selecting individuals for clinical trials testing therapies to prevent or delay clinical diagnosis of T1D (5).

However, in prospective studies investigators have observed that antibody levels can vary over time and individuals can acquire additional autoantibodies or previously positive autoantibodies can revert to negative (6). The current definition of stage 1 does not specify whether persistence or confirmation of multiple antibody status is required for identification of those at highest risk of progression to symptomatic disease. Confirmation of the first antibody positivity ideally within 3 months is important, since the accuracy of autoantibody tests can vary between laboratories and target antigens. But population screening demands an acceptable and evidence-based monitoring and care program that reflects and responds to risk and rate of progression to clinical disease. Recent reporting from the Fr1da study included which proportion of children identified as having multiple antibodies through general population screening are initially classified in the three different T1D stages (7). Approximately 90% of children with early-stage T1D were at stage 1. One-half of those with stage 2 T1D progressed to stage 3 within 2 years, while progression to stage 3 was much slower in the children with stage 1 T1D. The rate of progression is not the same for all, and there is a need to introduce an acceptable follow-up pathway that informs individuals about their short- and mid-term progression likelihood.

Frohnert et al. (8) provide evidence that follow-up over 2 years can differentiate which of these intermediate-risk individuals will enter the highest-risk category and which will continue to remain at lower risk, indicating that ongoing measurement of islet autoantibodies has clinical utility. These results have important implications for refining diagnostic criteria for stage 1 T1D and emphasize the need for confirmation of antibody positivity. Short-term follow-up over 2 years further refines risk (Fig. 1). In analyses of combined and harmonized prospective birth cohort studies of >16,000 children at risk for T1D enrolled by age 2.5 years, 865 were positive for one or more autoantibody and 537 (62%) progressed to stage 3 T1D after a 15-year follow-up. Ontology of islet autoantibody patterns co-occurrence, and persistence of autoantibodies defined by increasing stringency of positivity for multiple islet autoantibodies, was used to estimate the risk of progression to stage 3 T1D. The 15-year cumulative incidence of diabetes was highest with 88% (95% CI 85–92) in those with the most stringent definition, i.e., requiring not only concurrent presence of two or more

[1]*Unit of Paediatric Endocrinology and Diabetes, Hospital Dona Estefânia, Lisbon, Portugal*
[2]*Comprehensive Health Research Centre, NOVA Medical School, Universidade NOVA de Lisboa, Lisbon, Portugal*
[3]*Children's Hospital AUF DER BULT, Hannover, Germany*
[4]*Hannover Medical School, Hannover, Germany*

Corresponding author: Thomas Danne, danne@hka.de

See accompanying article, p. 1753.

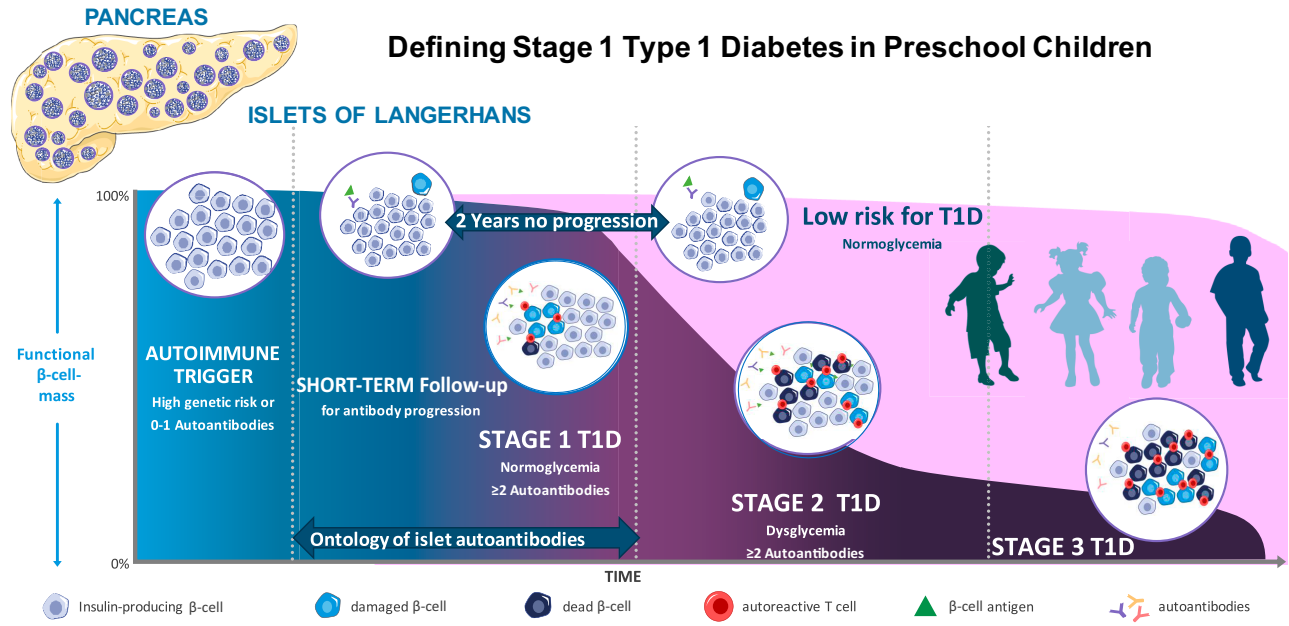

Figure 1—Defining stage 1 T1D in preschool children.

autoantibodies but also persistence of at least two of those autoantibodies at the next visit. Intermediate risk was considered for two different scenarios: if multiple positive autoantibodies were detected at the same visit, without requirement of persistence or secondly, if multiple positive autoantibodies were found at one visit, and at least one was positive at two consecutive visits. Definitions that do not require persistence of multiple autoantibodies but still include at least one visit with multiple positive autoantibodies at the same visit identify a group at moderate risk. Finally, individuals whose multiple antibodies are neither contemporaneous nor persistent have an 18% (5–40), albeit the lowest, cumulative incidence of stage 3 T1D.

Of note, loss of a single autoantibody in those who are positive for multiple antibodies with all three autoantibodies confers a short-term increase in risk of progression. The authors do not speculate on potential explanations for this observation. Many individuals with long-standing T1D no longer have islet immunity present in their blood (9). As has been observed before (10,11), young age was significantly associated with time from seroconversion to a more stringent definition of multiple antibody status and to stage 3 T1D, emphasizing the need to detect T1D early in life. In addition, HLA markers (11), or appearance of insulin autoantibody first (12), have been shown to influence the progression rate (10–14). Indeed, with use of IA-2 antigen titer, HbA_{1c}, and glucose at 90 min during oral glucose tolerance testing, a progression likelihood score for the 2-year progression was proposed, which could allow a substaging of stage 1 into slow (stage 1a) or fast (stage 1b) T1D progression (7).

As the momentum for screening children in the general population grows, the study by Frohnert et al. provides important guidance for follow-up. Monitoring at 6- to 12-monthly intervals has been used for participants in prevention trials. More frequent monitoring can be indicated for children who screen positive before 3 years of age and are at high risk of progression. However, monitoring of antibodies for younger and older adults may be different from that in children and adolescents, and limited data are available on non-White populations. Preliminary data on psychological aspects of screening were gathered in previous projects (Fr1da [15], The Environmental Determinants of Diabetes in the Young [TEDDY] [16], and Global Platform for the Prevention of Autoimmune Diabetes [GPPAD] [17]). As 9 of 10 families in a population screening will have no prior knowledge of T1D, key elements to reduce anxiety and stress are information and education, about the relevance of antibody results and eventual development of T1D, that are appropriate for families and children. While initial categorization identifies individuals at highest risk, short-term follow-up over 2 years may help with stratification of evolving risk, especially for those with less stringent definitions of multiple antibodies status.

With the proposed strategy, a first step for a personalized approach is taken where monitoring frequency and/or pharmacological interventions and psychological counseling strategies could then vary based on the stratified definition of stage 1 in islet autoantibody–positive individuals. A limitation of the present definition of stage 1 T1D is that only a binary outcome (positive or negative) of autoantibody measurement was used. Indeed, autoantibody titer levels can be an important predictor of risk. Furthermore, the importance of individual autoantibodies and their pattern of appearance and disappearance in assessment of risk has been shown (18). In this regard, future analysis needs to include ZnT8 or islet cytoplasmic antibodies that were not included in the analysis. Other future approaches may include genetic risk stratification as T1D has a strong polygenic component.

Thus, the definition of stage 1 T1D proposed by Frohnert et al. could help with earlier intervention—starting in stage 1—as this would allow more β-cell function to be preserved. The European clinical trial platform INNODIA has developed a master protocol and a platform study design as well as trialing adaptive elements to facilitate studies in stage 3 T1D (19–21). In terms of clinical care, being able to

intervene in stage 1 would allow more time to switch to second- or third-line medication if an individual fails first-line treatment, as is recommended in other autoimmune diseases (22). There is increasing evidence that progression can be predicted with nuanced analysis of continuous glucose monitoring data (23). Thus, once stage 1 is clearly defined, advanced modeling of glucose, insulin, and c-peptide parameters allows monitoring of the disease modulation (24,25). Personalized approaches refining our definitions and stratification of early-stage T1D may therefore be important for guidance for counseling individuals identified through population screening.

Duality of Interest. C.L. reports grants and speaker's honoraria from Abbott, Ipsen, and Sanofi. T.v.d.B. reports speaker's honoraria or consulting fees from Novo Nordisk, Medtronic, VitalAire, and Acensia. T.D. has received speaker's honoraria and research support from or has consulted for Abbott, AstraZeneca, Boehringer Ingelheim, Dexcom, Lilly, Medtronic, Novo Nordisk, ProventionBio, Roche, Sanofi, and Vertex Pharmaceuticals and is a shareholder of DreaMed. No other potential conflicts of interest relevant to this article were reported.

References

1. Sims EK, Bundy BN, Stier K, et al.; Type 1 Diabetes TrialNet Study Group. Teplizumab improves and stabilizes beta cell function in antibody-positive high-risk individuals. Sci Transl Med 2021;13:eabc8980
2. Forlenza GP, McVean J, Beck RW, et al.; CLVer Study Group. Effect of verapamil on pancreatic beta cell function in newly diagnosed pediatric type 1 diabetes: a randomized clinical trial. JAMA 2023;329:990–999
3. Besser REJ, Bell KJ, Couper JJ, et al. ISPAD clinical practice consensus guidelines 2022: stages of type 1 diabetes in children and adolescents. Pediatr Diabetes 2022;23:1175–1187
4. ElSayed NA, Aleppo G, Aroda VR, et al.; American Diabetes Association. 2. Classification and Diagnosis of Diabetes: *Standards of Medical Care in Diabetes—2023*. Diabetes Care 2023;46(Suppl. 1): S19–S40
5. Karpen SR, Dunne JL, Frohnert BI, et al.; Type 1 Diabetes Consortium. Consortium-based approach to receiving an EMA qualification opinion on the use of islet autoantibodies as enrichment biomarkers in type 1 diabetes clinical studies. Diabetologia 2023;66:415–424
6. Barker JM, Barriga KJ, Yu L, et al.; Diabetes Autoimmunity Study in the Young. Prediction of autoantibody positivity and progression to type 1 diabetes: Diabetes Autoimmunity Study in the Young (DAISY). J Clin Endocrinol Metab 2004;89: 3896–3902
7. Weiss A, Zapardiel-Gonzalo J, Voss F, et al.; Fr1da-study group. Progression likelihood score identifies substages of presymptomatic type 1 diabetes in childhood public health screening. Diabetologia 2022;65:2121–2131
8. Frohnert BI, Ghalwash M, Li Y, et al.; T1DI Study Group. Refining the definition of stage 1 type 1 diabetes: an ontology-driven analysis of the heterogeneity of multiple islet autoimmunity. Diabetes Care 2023;46:1753–1761
9. Williams CL, Fareed R, Mortimer GLM, et al.; BOX Study Group. The longitudinal loss of islet autoantibody responses from diagnosis of type 1 diabetes occurs progressively over follow-up and is determined by low autoantibody titres, early-onset, and genetic variants. Clin Exp Immunol 2022;210:151–162
10. Bonifacio E, Weiß A, Winkler C, et al.; TEDDY Study Group. An age-related exponential decline in the risk of multiple islet autoantibody seroconversion during childhood. Diabetes Care 2021;44:2260–2268
11. Anand V, Li Y, Liu B, et al.; T1DI Study Group. Islet autoimmunity and HLA markers of presymptomatic and clinical type 1 diabetes: joint analyses of prospective cohort studies in Finland, Germany, Sweden, and the U.S. Diabetes Care 2021;44:2269–2276
12. Bingley PJ, Boulware DC, Krischer JP; Type 1 Diabetes TrialNet Study Group. The implications of autoantibodies to a single islet antigen in relatives with normal glucose tolerance: development of other autoantibodies and progression to type 1 diabetes. Diabetologia 2016;59:542–549
13. Vehik K, Lynch KF, Schatz DA, et al.; TEDDY Study Group. Reversion of β-cell autoimmunity changes risk of type 1 diabetes: TEDDY study. Diabetes Care 2016;39:1535–1542
14. Krischer JP, Liu X, Lernmark Å, et al.; TEDDY Study Group. Predictors of the initiation of islet autoimmunity and progression to multiple autoantibodies and clinical diabetes: the TEDDY study. Diabetes Care 2022;45:2271–2281
15. Ziegler AG, Kick K, Bonifacio E, et al.; Fr1da Study Group. Yield of a public health screening of children for islet autoantibodies in Bavaria, Germany. JAMA 2020;323:339–351
16. Smith LB, Liu X, Johnson SB, et al.; TEDDY study group. Family adjustment to diabetes diagnosis in children: can participation in a study on type 1 diabetes genetic risk be helpful? Pediatr Diabetes 2018;19:1025–1033
17. Houben J, Janssens M, Winkler C, et al.; GPPAD study group. The emotional well-being of parents with children at genetic risk for type 1 diabetes before and during participation in the POInT-study. Pediatr Diabetes 2022;23:1707–1716
18. Kwon BC, Achenbach P, Anand V, et al. Islet autoantibody levels differentiate progression trajectories in individuals with presymptomatic type 1 diabetes. Diabetes 2022;71:2632–2641
19. Dunger DB, Bruggraber SFA, Mander AP, et al.; INNODIA consortium. INNODIA Master Protocol for the evaluation of investigational medicinal products in children, adolescents and adults with newly diagnosed type 1 diabetes. Trials 2022;23:414
20. Wilhelm-Benartzi CS, Miller SE, Bruggraber S, et al. Study protocol: minimum effective low dose: anti-human thymocyte globulin (MELD-ATG): phase II, dose ranging, efficacy study of anti-thymocyte globulin (ATG) within 6 weeks of diagnosis of type 1 diabetes. BMJ Open 2021;11: e053669
21. Anderson RL, DiMeglio LA, Mander AP, et al. Innovative designs and logistical considerations for expedited clinical development of combination disease-modifying treatments for type 1 diabetes. Diabetes Care 2022;45:2189–2201
22. Smolen JS, Landewé RBM, Bijlsma JWJ, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis 2020;79:685–699
23. Wilson DM, Pietropaolo SL, Acevedo-Calado M, et al.; Type 1 Diabetes TrialNet Study Group. CGM metrics identify dysglycemic states in participants from the TrialNet Pathway to Prevention study. Diabetes Care 2023;46:526–534
24. Koskinen MK, Mikk ML, Laine AP, et al. Longitudinal pattern of first-phase insulin response is associated with genetic variants outside the class II HLA region in children with multiple autoantibodies. Diabetes 2020;69:12–19
25. Galderisi A, Evans-Molina C, Martino M, Caprio S, Cobelli C, Moran A. β-Cell function and insulin sensitivity in youth with early type 1 diabetes from a 2-h 7-sample OGTT. J Clin Endocrinol Metab 2023;108:1376–1386