EPIDEMIOLOGY/HEALTH SERVICES RESEARCH

Rising Hemoglobin A_{1c} in the Nondiabetic Range Predicts Progression of Type 1 Diabetes As Well As Oral Glucose Tolerance Tests

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Kendra Vehik,[1] David Boulware,[1] Michael Killian,[2] Marian Rewers,[3] Richard McIndoe,[4] Jorma Toppari,[5] Åke Lernmark,[6] Beena Akolkar,[7] Anette-G Ziegler,[8] Henry Rodriguez,[9] Desmond A. Schatz,[10] Jeffrey P. Krischer,[1] and William Hagopian,[2] for the TrialNet Study Group and TEDDY Study Group*

OBJECTIVE

Biomarkers predicting risk of type 1 diabetes (stage 3) among children with islet autoantibodies are greatly needed to prevent diabetic ketoacidosis and facilitate prevention therapies.

RESEARCH DESIGN AND METHODS

Children in the prospective The Environmental Determinants of Diabetes in the Young (TEDDY) study (n = 707) with confirmed diabetes-associated autoantibodies (GAD antibody, IA-2A, and/or insulin autoantibody) and two or more HbA_{1c} measurements were followed to diabetes or median age 11.1 years. Once confirmed autoantibody positive, HbA_{1c} was measured quarterly. Cox models and receiver operative characteristic curve analyses revealed the prognostic utility for risk of stage 3 on a relative HbA_{1c} increase from the baseline visit or an oral glucose tolerance test (OGTT) 2-h plasma glucose (2-hPG). This HbA_{1c} approach was then validated in the Type 1 Diabetes TrialNet Pathway to Prevention Study (TrialNet) (n = 1,190).

RESULTS

A 10% relative HbA_{1c} increase from baseline best marked the increased risk of stage 3 in TEDDY (74% sensitive; 88% specific). Significant predictors of risk for HbA_{1c} change were age and HbA_{1c} at the baseline test, genetic sex, maximum number of autoantibodies, and maximum rate of HbA_{1c} increase by time of change. The multivariable model featuring a HbA_{1c} ≥10% increase and these additional factors revealed increased risk of stage 3 in TEDDY (hazard ratio [HR] 12.74, 95% CI 8.7–18.6, $P < 0.0001$) and TrialNet (HR 5.09, 95% CI 3.3–7.9, $P < 0.0001$). Furthermore, the composite model using HbA_{1c} ≥10% increase performed similarly to an OGTT 2-hPG composite model (TEDDY area under the curve [AUC] 0.88 and 0.85, respectively) and to the HbA_{1c} model in TrialNet (AUC 0.82).

CONCLUSIONS

An increase of ≥10% in HbA_{1c} from baseline is as informative as OGTT 2-hPG in predicting risk of stage 3 in youth with genetic risk and diabetes-associated autoantibodies.

The incidence of autoimmune type 1 diabetes rose 1.4% annually from 2002 to 2012 in youth <20 years of age, with the greatest increase in those <5 years of age (1).

[1]Health Informatics Institute, Morsani College of Medicine, University of South Florida, Tampa, FL
[2]Pacific Northwest Research Institute, Seattle, WA
[3]Barbara Davis Center for Childhood Diabetes, University of Colorado, Aurora, CO
[4]Center for Biotechnology and Genomic Medicine, Medical College of Georgia, Georgia Regents University, Augusta, GA
[5]Research Centre for Integrative Physiology and Pharmacology, Institute of Biomedicine, University of Turku, and Department of Pediatrics, Turku University Hospital, Turku, Finland
[6]Department of Clinical Sciences, Lund University/Clinical Research Centre, Skane University Hospital, Malmö, Sweden
[7]National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD
[8]Institute of Diabetes Research, Helmholtz Zentrum München, and Klinikum rechts der Isar, Technische Universität München, and Forschergruppe Diabetes e.V. Neuherberg, Germany
[9]USF Diabetes and Endocrinology Center, Morsani College of Medicine, University of South Florida, Tampa, FL
[10]Diabetes Center of Excellence, University of Florida, Gainesville, FL

Corresponding authors: Kendra Vehik, kendra.vehik@epi.usf.edu, and William Hagopian, wah@uw.edu

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*A complete list of the TrialNet Study Group and TEDDY Study Group can be found in the supplementary material online.

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Type 1 diabetes has been widely shown to be predictable by islet autoantibody testing (2–4). These autoantibodies may be present long before the onset of dysglycemia or clinical diabetes (stage 3) and do not accurately predict when hyperglycemia and the need for prompt insulin therapy will occur. Advanced knowledge of this timing is of key importance to enable close glycemic monitoring and early detection of symptoms to effectively prevent diabetic ketoacidosis at onset (5,6). Further, this approach enables application of immunotherapy at a time when more β-cell mass remains than at stage 3.

Many types of biomarkers have been evaluated to predict timing of disease progression in autoantibody-positive children (7,8). Along with HLA DR-DQ, there are >50 other genetic loci significantly associated with type 1 diabetes; yet, even combinations have not allowed prediction of disease progression in individuals (9). We now know of autoantibodies to ≥10 β-cell antigens, but most are secondary or spreading autoantigens, and their patterns, epitopes, and isotypes have not yielded sufficiently informative timing information. Neither measures of islet-specific $CD4^+$ and $CD8^+$ T cells accessible in peripheral blood (10) nor circulating metabolites (11) have provided consistent individual measures of disease progression. Even declining C-peptide is a late change that is not sensitive in the preonset period (12).

Evidence has revealed that dysglycemia occurs months to years prior to stage 3, and monitoring glycemia may offer reliable prediction of stage 3. However, fasting blood glucose, while part of standardized guidelines, may be insensitive to predict stage 3 (13). Random self-monitored capillary blood glucose levels are sometimes useful, but compliance can be difficult for families without a current patient with diabetes, where most new cases will arise. Oral glucose tolerance tests (OGTTs), as a sensitive measure of dysglycemia, are an important part of the official diagnostic guidelines (14), but their extended time course is challenging to complete in standard pediatric clinic settings. Continuous glucose monitors reveal detailed glycemia levels, excursions, and patterns, and can accurately predict impending stage 3 (15), but require greater clinician involvement and greater device costs.

Glycohemoglobin (HbA_{1c}) measurements require only a single fingerstick sample, are inexpensive, widely available, and familiar to clinicians. The American Diabetes Association and World Health Organizations, along with an International Expert Committee, have established an HbA_{1c} value for diagnosis of diabetes of ≥6.5%, largely based on adult type 2 diabetes data (14). However, since HbA_{1c} measures average blood glucose over the prior 6 to 12 weeks, it cannot reflect acute changes in the glycemic milieu. For this reason, single HbA_{1c} measurements have not been useful, even at onset, to diagnose childhood diabetes in most settings (16).

Rather than a single measure, increases in HbA_{1c} were first suggested to be informative in 2006. There was a significant HbA_{1c} increase among autoantibody-positive progressors to stage 3 from a baseline of 5.1%, although no set criteria were established, perhaps because only annual HbA_{1c} data were available (17). More recently, HbA_{1c} values were shown to average 5.7% in 10 progressors versus 5.3% in 10 nonprogressors, while continuous glucose monitoring (CGM) and self-monitoring of blood glucose (SMBG) were deemed more useful (18). A report from the Finnish Diabetes Prediction and Prevention (DIPP) study suggested a 10% increase was predictive (19), although another study found a 10% increase insufficient and recommended using a 20% increase (20).

Given these findings, the current analysis assessed whether a relative change in HbA_{1c} over time was predictive of stage 3 in an international multisite pediatric population and further validated in a large, independent study of relatives to patients with type 1 diabetes. The specific aims were to *1*) evaluate whether a change in HbA_{1c} predicted risk of stage 3; *2*) identify specific diabetes-related risk factors in TEDDY that predict a change in HbA_{1c}; *3*) determine whether a rapid change in HbA_{1c} increased the estimated risk of stage 3; and *4*) compare HbA_{1c}-based to OGTT-based composite predictors to assess their relative merits.

RESEARCH DESIGN AND METHODS

Study Design and Participants

The primary population is derived from the multinational TEDDY prospective cohort (21) and the validating population from the Type 1 Diabetes TrialNet Pathway to Prevention Study (TrialNet) (22). In both studies, eligible participants are <21 years of age, are positive for one or more islet autoantibodies, and have undergone at least two serial HbA_{1c} measurements. Stage 3 type 1 diabetes is defined using the American Diabetes Association criteria (14). The primary objective assessed the prognostic utility of a relative change in HbA_{1c} on risk of stage 3. Relative change in HbA_{1c} is the calculated percentage change at each serial measure up to the stage 3 diagnosis from the baseline HbA_{1c} measure. HbA_{1c} measures collected at diagnosis or postdiagnosis are excluded. The details of these two studies have previously been described (22,23).

TEDDY Study

Children are screened at birth for high-risk HLA genotypes (24) and, if eligible, enrolled <4 months of age between 2004 and 2010 and then followed through December 2019 for this analysis. The study enrolled 8,676 children (89% general population, 11% first-degree relatives), of whom 832 developed islet autoimmunity. TEDDY defined autoantibody positive as positive for at least one autoantibody (GAD antibody [GADA], IA-2A, or insulin autoantibody [IAA]) on two consecutive visits confirmed by both TEDDY core laboratories (21). HbA_{1c} was collected at first appearance of autoantibodies starting as early as the 12-month visit. HbA_{1c} was collected every 3 months if the child remained autoantibody positive. Otherwise, if a child reverted to antibody negative for 12 months, collection of these measures stopped. OGTT was performed every 6 months in children with two or more autoantibodies starting at age 3 years. The OGTT 2-h plasma glucose (2-hPG), the part of the OGTT typically used to assess glucose tolerance, is evaluated as a prognostic comparison with relative change in HbA_{1c} on risk of stage 3 in a subgroup of children who had both HbA_{1c} and OGTT measures available.

TrialNet Study

From February 2004 through December 2012, the TrialNet study screened islet autoantibodies in 112,280 individuals with a relative with type 1 diabetes. If an individual is positive for GADA, IAA, or IA-2A, they are tested for cytoplasmic islet cell antibodies and zinc transporter 8 autoantibodies (available from 2012 onward) on the same sample. After confirmation of

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autoantibody positivity and based on number of autoantibodies, participants are assessed every 6–12 months, which includes HbA_{1c} and repeat autoantibody testing. All assays were performed at a central core laboratory (22).

HbA_{1c} Measurement

TEDDY and TrialNet use a single core laboratory to measure HbA_{1c} using the NGSP-certified method. TEDDY samples were tested at the Diagnostic Diabetes Laboratory in Columbia, MO. TrialNet samples were processed at the Northwest Lipids Research Laboratory in Seattle, WA. Both laboratories measured HbA_{1c} using ion-exchange high-performance liquid chromatography with G7 and G8 autoanalyzers (TOSOH Bioscience, San Francisco, CA) standardized using the Diabetes Control and Complications Trial reference method (imprecision coefficient of variation $<$1.3%). For local collection at diagnosis, the U.S. and Canadian NGSP reference ranges and most European sites used International Federation of Clinical Chemistry and Laboratory Medicine or DCCT ranges. The Swedish (SWE) clinical centers used the Mono S normal ranges or International Federation of Clinical Chemistry and Laboratory Medicine reference ranges. These measures were converted to NGSP reference ranges for comparison in the analyses (SWE Mono S: NGSP% = [0.923 × SWE%] + 1.345) (25).

Statistical Analysis

We assessed a relative change in HbA_{1c} from a baseline measure taken within 3 months after a child first seroconverted to positivity for islet autoantibody(s) in TEDDY or from the time of first HbA_{1c} measure (baseline) in TrialNet. Mann-Whitney *U* tests compared median values. Kaplan-Meier curves depict proportions reaching a specific relative change in HbA_{1c} and proportions, with or without stage 3. Multivariable Cox proportional hazards models assessed known risk factors associated with specific relative changes from baseline in HbA_{1c} (5, 10, or 20%). We evaluated known risk factors, including family history of type 1 diabetes (father, mother, or sibling), HLA DR3/4 or other genotype, age at baseline HbA_{1c} visit, HbA_{1c} value at baseline visit, genetic sex, number of autoantibodies at time of relative change in HbA_{1c}, first-appearing IAA versus GADA, and maximum rate of HbA_{1c} change and interactive effects. The maximum rate of change in relative HbA_{1c} from baseline was defined as the greatest percent HbA_{1c} change between consecutive HbA_{1c} measures up to the time when the overall HbA_{1c} change threshold percentage was achieved over time from baseline. Number of autoantibodies was calculated as the maximum number of autoantibodies up to the specific percentage change in HbA_{1c}. Multivariable Cox proportional hazards models evaluated the risk of stage 3 based on whether or not a specified relative change in HbA_{1c} was reached. These models were adjusted for age at HbA_{1c} baseline visit, HbA_{1c} baseline value, maximum rate of change, and number of autoantibodies by the time the HbA_{1c} increase was achieved. Family history of type 1 diabetes, sex, and HLA DR3/DR4 genotype were assessed as binary variables. Receiver operating characteristic (ROC) curves reveal the prognostic performance of a relative change in HbA_{1c} or OGTT 2-hPG. Optimal thresholds for relative change in HbA_{1c} and OGTT 2-hPG were identified using the Youden index (i.e., maximum of the sum of the sensitivity and specificity) (26). Prognostic composite scores consisting of specific associated risk factors, including the threshold of $\geq$10% HbA_{1c} increase or OGTT 2-hPG $\geq$8 mmol/L on the risk of stage 3 were evaluated by time-varying ROC models using the inverse probability of censoring weighting method from the time of meeting the threshold or baseline value if the threshold is unmet. External validation of a $\geq$10% increase in HbA_{1c} from the baseline collected HbA_{1c} on risk of stage 3 used the TrialNet study. Data were analyzed on SAS 9.4 software (SAS Institute, Cary, NC) and GraphPad Prism 7.04 (GraphPad Software, San Diego, CA) was used for figures. Two-tailed *P* values $<$0.05 were considered significant.

RESULTS

This analysis includes 707 TEDDY participant children who met the inclusion criteria as of 31 December 2019. The median age at diagnosis or last visit was 11.1 (interquartile range 9.0–12.8) years. Of these 707 children, 304 (43.0%) remained single-autoantibody positive throughout the follow-up and 403 (57.0%) developed multiple autoantibodies. During follow-up, 235 (33.2%) developed stage 3 (213 [52.9%] from the group with multiple autoantibodies and 22 [7.2%] from those with a single autoantibody). Characteristics by stage 3 status are summarized for TEDDY participants in Supplementary Table 1.

In similar fashion, 1,190 TrialNet youth who met the inclusion criteria as of 31 December 2012 are included in this analysis. The median age at diagnosis or last visit was 12.95 years. During follow-up, 193 (16.2%) developed clinical type 1 diabetes (180 [21.6%] from those with multiple autoantibodies [*n* = 834] and 13 [3.7%] from those with a single autoantibody [*n* = 356]). Characteristics of these TrialNet participants are reported in Supplementary Table 2.

Determining Optimum Size of HbA_{1c} Percentage Increase and OGTT 2-hPG Level to Predict Stage 3 in TEDDY

Using only the glycemic measure itself in ROC curve analysis, the most predictive overall extent of HbA_{1c} increase from baseline was found to be 10% based on maximizing the Youden J statistic (Fig. 1*A*). This increase was 73.6% sensitive and 88.3% specific to mark future stage 3 occurring during follow-up observation. The positive predictive value (PPV) was 76%. In a similar manner, for the OGTT, the most predictive 2-hPG level was $\geq$8 mmol/L, 73.0% sensitive and 82.4% specific with a PPV of 79%, to mark future stage 3 occurring during follow-up observation (Fig. 1*B*).

Factors Associated With a ≥10% Relative Change in Percent HbA_{1c}

We next sought to identify diabetes-related primary risk factors significantly associated with an increase in HbA_{1c} from baseline (Supplementary Table 3). An older age at the baseline test was associated with a decreased risk of achieving a $\geq$10% increase in HbA_{1c} for both studies (hazard ratio [HR] 0.92, overall $P <$ 0.014). Further, a lower HbA_{1c} level at the baseline test was associated with an increased risk of achieving a $\geq$10% increase in HbA_{1c} ($P <$ 0.0001 for both studies). The risk of a relative change in HbA_{1c} also increased with a greater number of autoantibodies present by the time that the $\geq$10% HbA_{1c} increase was achieved (TEDDY: HR 1.87, 95% CI 1.6–2.2, $P <$ 0.0001; TrialNet: HR 1.97, 95% CI 1.6–2.5, $P <$ 0.0001). A greater maximum rate of change between repeated HbA_{1c} measures from baseline

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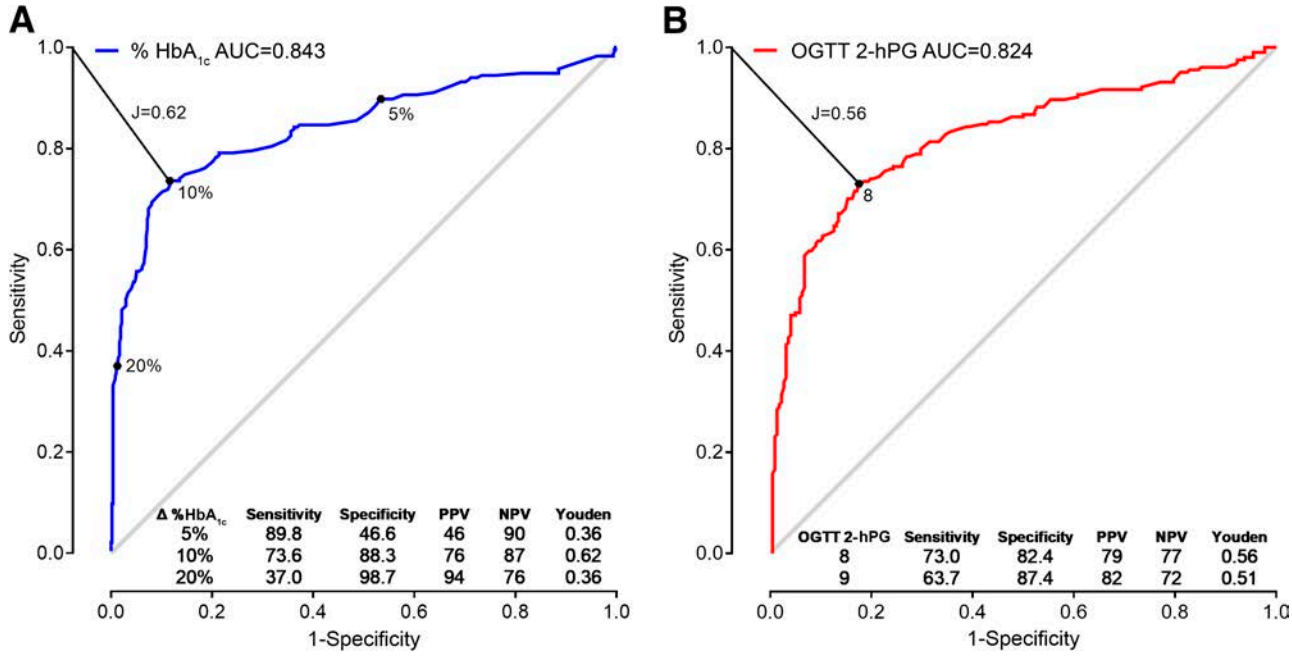

Figure 1—Identification of optimal thresholds and evaluation of percent HbA_{1c} increase from baseline HbA_{1c} (*A*) and OGTT 2-hPG (*B*) optimal thresholds as a prognostic for progression to type 1 diabetes in the TEDDY children. For the HbA_{1c}, n = 707 and for the OGTT n = 426. NPV, negative predicative value.

increased the risk of a ≥10% change in HbA_{1c} ($P < 0.0001$ for both studies). For unknown reasons, female children had a lower likelihood of HbA_{1c} risk in TEDDY (HR 0.72, 95% CI 0.6–0.9, P = 0.009), but not in TrialNet. Having a family history of type 1 diabetes was not associated with an HbA_{1c} change (P = 0.39). We also explored interactions of the above factors and found that a younger age at the HbA_{1c} baseline test significantly interacted with a greater number of autoantibodies to augment the risk of a ≥10% increase in HbA_{1c} from baseline in TEDDY children (HR 1.10, 95% CI 1.0–1.2, P = 0.021) (Supplementary Fig. 1). Finally, we assessed whether having a first-appearing IAA versus GADA associated with a change in HbA_{1c} and found no significant association in TEDDY (P = 0.37). Survival curves depicting the rate of achievement from time of seroconversion for 5%, 10%, and 20% overall increases in HbA_{1c} from baseline measurement are shown in Supplementary Fig. 2.

Change in HbA_{1c} Predicted Risk of Stage 3 in Youth

We used the identified optimum HbA_{1c} percentage increase (Fig. 1) in TEDDY adjusted for the factors that modify this change (Supplementary Table 3) in multivariable Cox proportional hazards models evaluating a ≥10% HbA_{1c} increase in TEDDY and TrialNet on risk of stage 3. Survival curves from this model applied to both studies are shown in Fig. 2. The multivariable model featuring a ≥10% increase in HbA_{1c} revealed a markedly increased risk of stage 3 in both TEDDY (HR 12.74, 95% CI 8.7–18.6, $P <$ 0.0001) and TrialNet (HR 5.09, 95% CI 3.3–7.9, $P < 0.0001$). We found that the

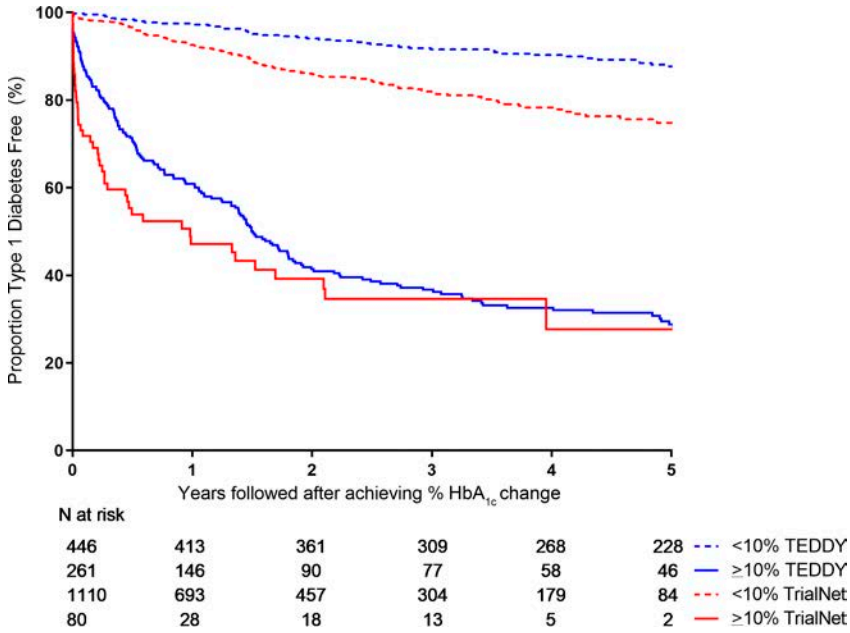

Figure 2—Multivariable Cox proportional hazards models evaluating ≥10% HbA_{1c} increase in TEDDY and TrialNet on progression to type 1 diabetes from time at ≥10% increase in HbA_{1c}. Reference is <10% HbA_{1c} increase. Models adjusted for age at HbA_{1c} baseline, HbA_{1c} baseline measure, number of autoantibodies at time of HbA_{1c} change, maximum rate of change from baseline, and genetic sex. A ≥10% increase in HbA_{1c} increases the risk of progression to type 1 diabetes in both the TEDDY (HR 12.74, 95% CI 8.7–18.6, $P < 0.0001$) and TrialNet (HR 5.09, 95% CI 3.3–7.9, $P < 0.0001$) studies.

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maximum rate of change between HbA_{1c} measures leading up to and including the visit at which the 10% threshold was met is associated with an increased risk of stage 3 (TEDDY: HR 1.34, 95% CI 1.2–1.5, $P < 0.0001$; TrialNet: HR 1.24, 95% CI 1.2–1.3, $P < 0.0001$). The median (interquartile range) years from the time the child had an HbA_{1c} ≥10% increase and progressed to stage 3 was 0.70 (0.2–1.7) in TEDDY and 0.16 (0.02–0.50) in TrialNet. In TEDDY, an older age at meeting the percent HbA_{1c} increase was associated with a lower risk of progressing within 2 years. Corresponding results for an overall 5%, 10%, or 20% HbA_{1c} increase are shown in Supplementary Fig. 3.

A Change in Percent HbA_{1c} Is as Good a Predictor of Future Stage 3 in a Young Population With Multiple Islet Autoantibodies As a Single OGTT 2-hPG

In TEDDY, the OGTT 2-hPG is measured only in children with multiple autoantibodies older than age 3, while HbA_{1c} is measured in those with any autoantibody. For this analysis, 426 children who had both HbA_{1c} and OGTT recorded are included. Most without an OGTT had only one autoantibody (n = 245), while 10 children were <3 years old and the remaining 26 did not have both measures available. The utility of a percentage increase in HbA_{1c} over baseline performed well as a prognostic measure in a young population, with an ROC area under the curve (AUC) of 0.825, essentially the same as the OGTT 2-hPG with an ROC AUC of 0.824 (Fig. 3*A*). Overall, 79% (n = 161 of 204) of the TEDDY children who had a ≥10% HbA_{1c} increase and 77% (n = 156 of 204) of those who had an OGTT 2-hPG ≥8 mmol/L developed stage 3 diabetes (Fig. 4). Given this, we developed a composite score for each of these measures to evaluate whether the performance could be improved. The time-varying ROC AUC performance of both the composite HbA_{1c} ≥10% increase model and the composite OGTT 2-hPG ≥8 mmol/L model were then determined for a range of time horizons summarized graphically in Fig. 3*B*, again showing remarkably comparable results over a wide range of time horizons (TEDDY integrated AUCs of 0.88 and 0.85, respectively). The composite score for HbA_{1c} ≥10% included whether or not threshold was met, age and HbA_{1c} at baseline measure, number of autoantibodies at time of HbA_{1c} change, and maximum rate of change up to HbA_{1c} ≥10% increase. The composite score for OGTT 2-hPG ≥8 mmol/L included whether or not the threshold was met, OGTT 2-hPG value at baseline, age when the threshold was met, family history of type 1 diabetes, and genetic sex. Assessment of known diabetes risk factors associated with a rise in OGTT ≥8 mmol/L are reported in Supplementary Table 4. These ROC AUC values were stable over a variety of time horizons after the glycemic criterion was achieved (Fig. 3*B*). The HbA_{1c} composite model performed equally well in the TrialNet population with an integrated AUC of 0.82 over 5-year horizons.

CONCLUSIONS

While the pathophysiology of type 1 diabetes is still not well understood, it is clear that stage 3 is heterogenous and associated with many factors. The time to stage 3 may be many years, and a practical, efficient way to monitor progression is an essential need. Monitoring HbA_{1c} over time is a promising early indicator to assess escalating risk in individuals at high-risk for type 1 diabetes from both the general population and those with a family history. Our findings

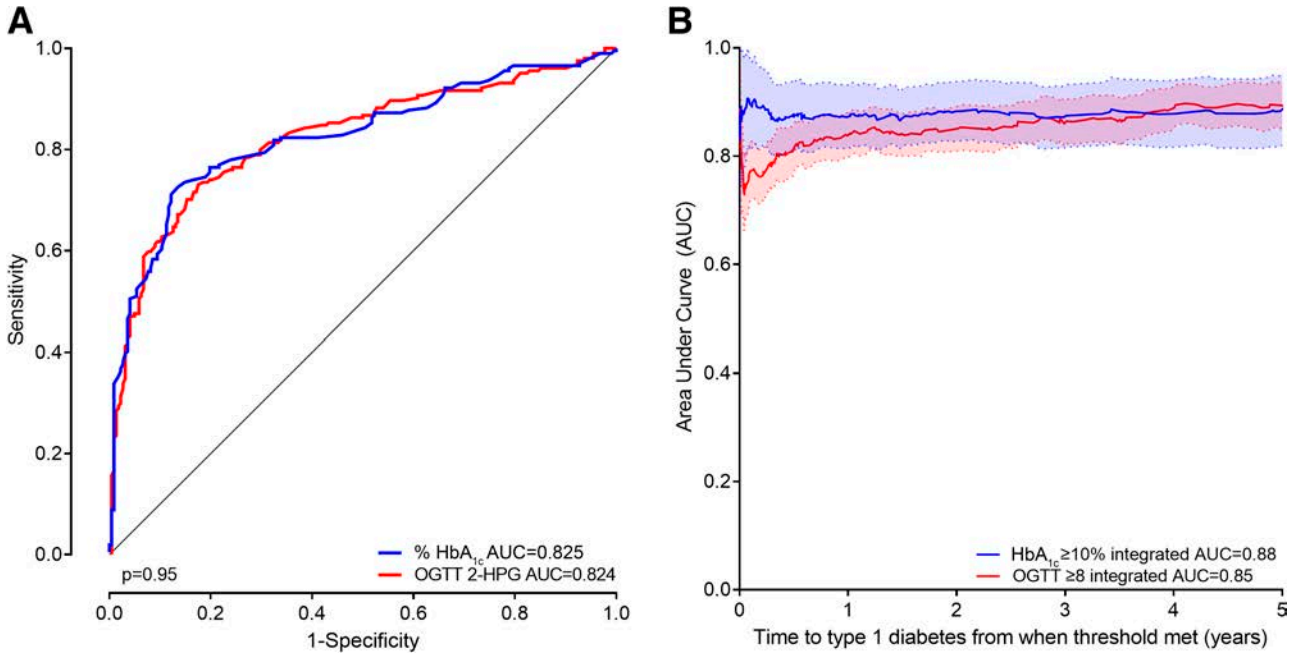

Figure 3—Evaluating the utility of percent HbA_{1c} increase and OGTT 2-HPG as prognostic measures on predicting progression of type 1 diabetes in a subset of TEDDY children with both percent HbA_{1c} change and OGTT data available (n = 426) (*A*) and composite score performance over increasing follow-up horizons (*B*). The composite score for HbA_{1c} ≥10% included whether or not the 10% increase in HbA_{1c} was achieved, the baseline HbA_{1c} value, the age at baseline HbA_{1c}, the maximum number of autoantibodies by time of the HbA_{1c} change, and maximum rate of change through the time of the HbA_{1c} ≥10% increase. Composite score for OGTT ≥8 mmol/L included whether or not the threshold was met, OGTT 2-hPG value at baseline, family history of type 1 diabetes, and genetic sex. Only significant covariates are included in the composite score models.

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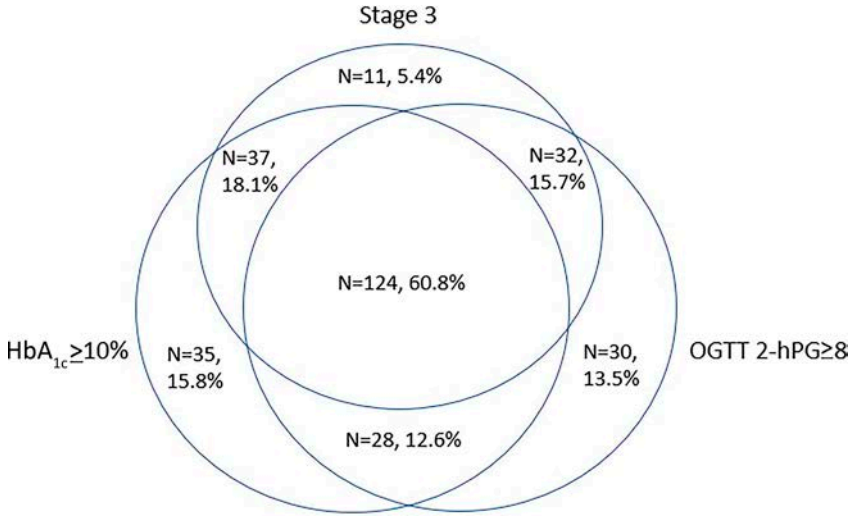

Figure 4—Venn diagram of the TEDDY children who met the HbA_{1c} ≥10% threshold and/or OGTT 2-hPG ≥8 mmol/L threshold and progressed to stage 3 (*n* = 204).

show that a relative increase of ≥10% in HbA_{1c} from baseline is as informative as OGTT 2-hPG in predicting risk of stage 3 in youth. Moreover, combined with age at the first HbA_{1c} test (related to age at seroconversion), baseline HbA_{1c} level, maximum rate of HbA_{1c} change, and number of islet autoantibodies, achieving a 10% increase from the baseline HbA_{1c} fits into a highly predictive composite model estimating risk of stage 3, with similar performance to a corresponding composite OGTT-based model. Periodic autoantibody surveillance of children with islet autoantibodies, including an HbA_{1c} measurement at each sampling, may be sufficient to estimate timing of onset within 2 years in most cases and requires no additional sampling by the clinician.

HbA_{1c} is among the 10 most common clinical laboratory tests performed in the U.S. (27). For HbA_{1c} measurements, the total allowable error currently ranges from ±5% (NGSP) to ±6% (College of American Pathologists), although a loosening of this requirement has been proposed (28). Direct comparisons of point-of-care testing to laboratory testing showed a mean relative difference of 2.1%, suggesting both point-of-care and laboratory-based tests can be quite precise and comparable (29), although variation in testing site or method could contribute to observed HbA_{1c} changes. In addition to variation in measurement, individual physiological variations in HbA_{1c} can result from increased red cell turnover (30) due to a number of hereditary, autoimmune, infectious, or chemical causes. A small variation of HbA_{1c} with season (amplitude 0.2–0.3%) has been described in many published studies over the last 25 years (31). Irrespective of blood glucose levels, a decrease in hemoglobin or iron, such as that caused by aberrant erythropoiesis, reduced iron absorption, or increased loss, has been associated with an increased HbA_{1c} level (32). Finally, several genetic loci are known to be associated with HbA_{1c} levels (33). Many of these loci are not associated with blood glucose levels, although their associations with hemolysis, erythropoiesis, or seasonal changes in physiology are not known.

When compared with OGTT, a single measure of HbA_{1c} was as predictive of type 2 diabetes as fasting plasma glucose or the OGTT 2-hPG in American Indian individuals 10–39 years of age in the Southwestern U.S. (34). Even in children, OGTT is not always clearly better than HbA_{1c} and especially CGM (18). However, for diabetes staging in large well-managed pediatric prediction studies, OGTT has provided very good predictive power (35,36). OGTT provides prognostic results from just one test, while the current HbA_{1c} method requires the additional information provided by sequential measurements. Yet, the OGTT test is challenging to perform in a primary care clinical setting or remotely by patient and family; whereas, HbA_{1c} is readily measured from one low-volume clinical or home sampling. Importantly, HbA_{1c} is an extremely common and accessible clinical test with modest cost and greater patient and provider familiarity than CGM or OGTT testing. In the setting of surveillance of islet autoantibody–positive children, often with stage 1 diabetes (37), quarterly blood sampling that adds HbA_{1c} testing to islet autoantibody testing is also reasonable from a logistical perspective. These children are at high risk of dysglycemia, and we believe they warrant such surveillance requiring overall blood draw volumes of <1 mL every 3 months. Our results suggest that HbA_{1c} monitoring can predict stage 3 with sufficient lead time for education and closer monitoring for earlier detection of metabolic decompensation. While a simple 10% rise from baseline in HbA_{1c} would be readily apparent to a clinician, obtaining a more accurate prognosis using the composite score might be facilitated by access to a simple and quick way to enter and use sequential HbA_{1c} and islet autoantibody results. A web-based application with a calculator format, for example, that is used for monogenic diabetes (38,39), could rapidly provide clinically interpretable prognostic information in those with genetic and familial risk screened for islet autoantibodies. In those who achieve this HbA_{1c} prognostic increase, the close monitoring of impending diabetes may then be an ideal setting for CGM (15,18) where ≥18% time spent at >140 mg/dL was shown to have a 100% PPV (15).

This study's strength is that TEDDY and TrialNet are large, prospective studies that collect metabolic measures on individuals at high genetic or familial risk of type 1 diabetes either quarterly in TEDDY or every 6–12 months in TrialNet. The short interval of collection in TEDDY provides an especially precise understanding of the variation of these measures across time and leading up to onset.

Yet, this analysis has some limitations. One is that our study population is at high genetic or familial risk. Although, most TEDDY children are from the general population, even those are selected from HLA genotypes that only account for 50% of general population type 1 diabetes cases. There are limits to generalizing these findings to all populations as these children are selected for elevated genetic or familial risk before further evaluation, which is typical of those

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who would be screened for interventional trials and observational studies. As with all predictive testing, consideration should be given to justifying screening programs for clinical use with focus on psychological impacts and long-term consequences (40). TEDDY did not start HbA_{1c} testing until late 2009, which was two-thirds of the way through TEDDY recruitment. Because of this and also because stage 3 is less common in infants and toddlers, fewer such cases were analyzed, and the results are less certain for very young onsets. Like any measure of glycemia, HbA_{1c} reflects not only β-cell function but also insulin sensitivity, as reflected by BMI, dietary choices, activity level, and ancestry, etc. The current participants in TEDDY were mostly prepubertal, a time when insulin sensitivity is generally high, so that elevated HbA_{1c} might be more reflective of endogenous insulinopenia. Our results must therefore be confirmed in studies of postpubertal onsets, albeit with care to differentiate type 1 prediabetes from type 2 prediabetes. Although ∼7% of TEDDY children were of African, Asian, or Hispanic ancestry (primarily from the U.S. sites), most were of European descent, and results should be confirmed in settings of more diverse ancestry. Finally, stage 3 was ascertained more promptly under the TEDDY and TrialNet protocols (often through OGTT or home SMBG) than might be expected during routine medical care, although not more promptly than what might be achieved by the ongoing glycemic surveillance that our approach implies.

Here, we show that change in HbA_{1c} is a useful noninvasive measure to predict the likelihood of stage 3 in a young population. Such HbA_{1c} surveillance might be part of a sequential multitiered approach consisting of *1*) genetic screening at birth; *2*) subsequent islet autoantibody cross-sectional screening with confirmation of positive results; *3*) ongoing islet autoantibody and HbA_{1c} surveillance and parental education in those with confirmed islet autoantibod(ies); and *4*) heightened glycemic surveillance (e.g., CGM or OGTT) and/or referral to immunotherapy trials in those that met the HbA_{1c} threshold during surveillance testing. Tier 3 above represents simpler glycemic surveillance than that specified in TEDDY or TrialNet protocols. This may improve compliance and lower costs to translate better to general medical care settings while preserving early diagnosis, lowered morbidity from diabetic ketoacidosis at onset, and opportunities for intervention therapy.

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