Hemoglobin A1c Patterns of Youth With Type 1 Diabetes 10 Years Post Diagnosis From 3 Continents

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abstract

OBJECTIVES: Distinct hemoglobin A1c (HbA1c) trajectories during puberty are identified in youth with established type 1 diabetes (T1D). We used data from 3 international registries to evaluate whether distinct HbA1c trajectories occur from T1D onset.

METHODS: Participants were <18 years old at diagnosis with at least 1 HbA1c measured within 12 months post diagnosis, along with ≥3 duration-year–aggregated HbA1c values over 10 years of follow-up. Participants from the Australasian Diabetes Data Network ($n = 7292$), the German-Austrian-Luxembourgian-Swiss diabetes prospective follow-up initiative (Diabetes Patienten Verlaufsdokumentation) ($n = 39\,226$) and the US-based Type 1 Diabetes Exchange Clinic Registry ($n = 3704$) were included. With group-based trajectory modeling, we identified unique HbA1c patterns from the onset of T1D.

RESULTS: Five distinct trajectories occurred in all 3 registries, with similar patterns of proportions by group. More than 50% had stable HbA1c categorized as being either low stable or intermediate stable. Conversely, ∼15% in each registry were characterized by stable HbA1c >8.0% (high stable), and ∼11% had values that began at or near the target but then increased (target increase). Only ∼5% of youth were above the target from diagnosis, with an increasing HbA1c trajectory over time (high increase). This group differed from others, with higher rates of minority status and an older age at diagnosis across all 3 registries ($P \leq .001$).

CONCLUSIONS: Similar postdiagnostic HbA1c patterns were observed across 3 international registries. Identifying the youth at the greatest risk for deterioration in HbA1c over time may allow clinicians to intervene early, and more aggressively, to avert increasing HbA1c.

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WHAT'S KNOWN ON THIS SUBJECT: In previous studies, researchers explored hemoglobin A1c (HbA1c) trajectories in youth with type 1 diabetes with at least 2-years disease duration. Analysis from 3 registries revealed that 5 trajectory-based clusters emerged from each registry, each with unique patterns of glycemia over time.

WHAT THIS STUDY ADDS: From type 1 diabetes onset, youth in 3 international registries followed 5 distinct HbA1c patterns. Two trajectories, ∼15% of each registry, had progressive deterioration in HbA1c. Thus, early identification of youth at the highest risk may be feasible, allowing intensification of services.

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Despite the data from the Diabetes Control and Complications Trial definitively revealing lower rates of microvascular complications in those receiving intensive insulin therapy, thereby setting the standard for the importance of achieving more targeted glycemia, this goal has remained elusive for many youth living with type 1 diabetes (T1D).[1,2] In a long-term follow-up of participants through the Epidemiology of Diabetes Complications study, researchers have further highlighted these benefits, with decreased rates of both microvascular and macrovascular complications.[3–5] Indeed, with long-term follow-up, the concept of metabolic memory has emerged, whereby the intensively treated group remains relatively protected from complications over time, compared with the conventionally treated group. Thus, the foundation for setting glycemic targets is undeniable.

Concerningly, a clear pattern of a rise in hemoglobin A1c (HbA1c) levels has emerged from the analysis of youth with T1D living in 8 high-income countries as they progress from childhood to adolescence.[6] Although the mean HbA1c varied among the countries, a 0.7% (8 mmol/mol) difference was noted between the youngest and oldest cohorts.[6] However, it is clear that the path of glycemic deterioration varies. Using data from the German and Austrian diabetes prospective follow-up registry (Diabetes Patienten Verlaufsdokumentation [DPV]), Schwandt et al[7] demonstrated that during this transition from childhood to young adulthood, 5 unique HbA1c trajectories emerged. Two of these groups demonstrated progressive deterioration in glycemic control and accounted for ∼20% of the 6433 patients studied.

Interestingly, in analysis of 3 registries assessing HbA1c, researchers corroborated these findings, with only approximately one-fourth of participants in each registry categorized as being in the low stable trajectory, consistent with being at glycemic target.[8] Notably, these analyses were conducted in participants aged 8–18 years who had at least 2 years of disease duration.[7,8] Because these data highlighted the path of HbA1c trajectory regardless of disease duration, the question then arises as to what is the trajectory from the time of diagnosis and if these patterns can be identified early in the course of T1D. Although intensive insulin therapy is offered to all patients living with T1D, if it were feasible to predict those at the greatest risk of progressive glycemic deterioration from the time of or soon after diagnosis, it is possible that a more individualized approach could be implemented in this high-risk group to ensure therapies offered are successful. This may be particularly beneficial in settings with limited resources, in which it may be best to use services in those at highest risk.

To explore whether these HbA1c trajectories are present from the time of diagnosis, the present analysis was conducted including data from 3 international registries: the Australasian Diabetes Data Network (ADDN), the German-Austrian-Luxembourgian-Swiss diabetes prospective follow-up initiative (DPV), and the US-based Type 1 Diabetes Exchange Clinic Registry (T1DX). Additionally, exploration of the characteristics associated with certain trajectories was also conducted because identification of those most at risk for glycemic deterioration could inform targeting interventions to those groups.

METHODS

Participants

To be included in the analysis, participants needed to be diagnosed with T1D before the age of 18 years. HbA1c values for each individual were aggregated for each 12-month period post diagnosis to create a series of "duration-year–aggregated HbA1c values." Participants were required to have 1 HbA1c value recorded during the first year after diagnosis and at least 3 duration-year–aggregated HbA1c values over 10 years of follow-up to be included in the analysis. Those with islet cell or pancreas transplants were excluded from the analysis. HbA1c values during pregnancy were also excluded.

Registries

ADDN

Comprising 20 pediatric and adult centers from Australia and New Zealand, the ADDN has a centralized and standardized prospective data collection system for those living with T1D.[9,10] Data are transmitted in a deidentified form twice yearly to a central database. Local institutional review boards (IRBs) oversee the ethical requirements for each participating clinical site.

DPV

Since its inception in 1995, the DPV registry uses a standardized computer-based documentation strategy to collate data on nearly 500 clinical centers located in Austria, Germany, Luxembourg, and Switzerland.[11,12] These data are anonymized and transmitted to the Ulm University (Ulm, Germany), where scientific analysis is conducted. Ethical approvals are held through the ethics committee of Ulm University and the local IRB of the participating centers.

T1DX

Established in 2010, the T1DX included >80 US-based pediatric

and adult endocrinology practices providing specialized diabetes care and, thus, was a non–population-based registry.[13,14] Patients at each clinic consented to participate in the registry, and local IRB approval was maintained at each participating site. Retrospective data, including HbA1c over previous 10 years, were collected at enrollment and then annually up to 2018 and transmitted to the Jaeb Center for Health Research, the registry coordinating center.

Exploratory Variables

The mean Diabetes Control and Complications Trial standardized HbA1c was used, aggregated for each participant for each year after the onset of T1D. For the first year after diagnosis, data were aggregated from 3 months to 1 year of disease duration, with a minimum of 1 measure required to be included in the analysis. HbA1c data in the 3 months after T1D diagnosis were excluded, given significant variability in HbA1c in the period immediately after diagnosis. Subsequently, for each year of follow-up, the aggregated HbA1c was used for analysis. By using the target range recommended by the International Society for Pediatric and Adolescent Diabetes and the American Diabetes Association, the HbA1c level was defined as being at target if it was ≤7.0% (≤53 mmol/mol).[8,15,16] For the purpose of categorization, near target was considered to be an HbA1c level of 7.0% to 7.5% (53–58 mmol/mol), with above target defined as an HbA1c level of >7.5% (>58 mmol/mol).

Demographic data on age at diagnosis, sex, and minority status were collected and were defined a priori as covariables of interest. The definition of minority groups varied among the registries on the basis of their standard approach to this aspect. For ADDN, ethnicity was defined according to the Australian Standard Classification of Cultural and Ethnic Groups,[17] and ethnic minority status was defined as other than white. For the DPV, minority status was based on either the patient or at least 1 parent being born outside of Germany, Austria, Luxembourg, or Switzerland. In the T1DX, participants who self-identified as other than white non-Hispanic were considered to be part of the minority group. To aid with determination of the frequency of adolescents in each cohort, an age-based threshold of >10 years was used for women, and a threshold of >11 years was used for men.

Statistical Methods

Group-based trajectory modeling based on Nagin, a semiparametric finite-mixture statistical technique that is used to analyze longitudinal data, was employed.[7,8,18–20] By using this technique, unique HbA1c trajectories following a similar pattern over time over the first 10 years of T1D diagnosis were identified among each registry. The number of trajectories was determined by using a stepwise forward approach, starting with 1 group and then adding further groups with the Bayesian information criteria and clinical judgement, conditional on the requirement that a trajectory must contain at least 5% of the study cohort.

To describe the trajectory groups among the registries, continuous covariates are presented as median with quartiles, for those in which the assumptions for normal distribution were not met, or mean and SD otherwise, and proportions were used for binary covariables. Kruskal-Wallis or χ^2 tests were used for unadjusted comparisons among trajectory groups.

Data analyses were performed by using SAS 9.4 (SAS Institute, Inc, Cary, NC). Trajectory analysis was performed by using the PROC TRAJ macro. A two-sided P value <.05 was considered significant.

RESULTS

Study Cohort

A total of 50 222 participants were included in the analysis (ADDN: 7292; DPV: 39 226; and T1DX: 3704). Sex distribution was similar across all 3 registries. Ages at diabetes diagnosis by registry were as follows: ADDN: 8.1 (interquartile range [IQR] 4.7–11.2) years; DPV: 8.8 (IQR 5.3–11.8]) years; and T1DX: 5.0 (IQR 3.0–8.0) years. Classification as a minority was noted in 10% of ADDN, 19% of DPV, and 19% of T1DX registry participants. The mean ± SD number of observations per participant by registry were as follows: ADDN: 6.2 ± 2.8; DPV: 7.5 ± 2.5; and T1DX: 10.7 ± 0.8.

HbA1c Trajectory Across T1D Duration

With group-based trajectory modeling, we identified 5 HbA1c trajectories with similar patterns and proportions emerging across all 3 registries (Fig 1): (1) low stable, (2) intermediate stable, (3) high stable, (4) target increase, and (5) high increase. Although trajectories were similar among the 3 registries, the median baseline HbA1c (aggregated for months 3–12 after diagnosis) differed by registry and were as follows: 7.4% (IQR 6.8–8.2) for ADDN, 6.9% (IQR 6.2–7.6) for DPV, and 7.7% (IQR 7.0–8.4) for T1DX.

A low stable A1c trajectory from disease onset was present in ∼25% of participants (ADDN: 22%; DPV: 27%; T1DX: 27%). Overall, ∼44% of participants demonstrated an intermediate stable trajectory with HbA1c near target, with the median aggregated HbA1c from 3 months to

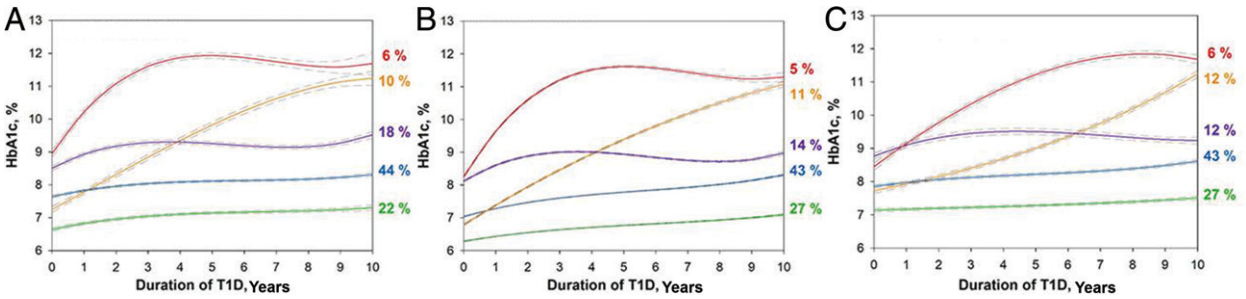

FIGURE 1

HbA1c trajectories with 95% confidence intervals among youth with T1D from the time of diagnosis. A, ADDN ($N = 7292$). B, The German-Austrian-Luxembourgian-Swiss diabetes prospective follow-up (DPV; $N = 39\,226$). C, US T1DX ($N = 3704$).

1 year being 7.6% (60 mmol/mol) for ADDN, 7.0% (53 mmol/mol) for DPV, and 7.8% (62 mmol/mol) for T1DX. A high stable trajectory, defined as the median aggregated HbA1c from 3 months to 1 year being >8.0% (64 mmol/mol), which remained stable at this above target range over time, was observed in 18% of the ADDN cohort, 14% of the DPV cohort, and 12% of the T1DX cohort. The target increase trajectory, characterized by a linear rise in HbA1c trajectory over time with rapid worsening of glycemia noted reaching above-target HbA1c levels within the first 2 years after diagnosis, was observed in 10% of the ADDN cohort, 11% of the DPV cohort, and 12% of the T1DX cohort. The high increase trajectory, characterized by progressive deterioration in glycemia, was followed by the fewest participants from each registry, accounting for ~5% of all participants.

Association Between HbA1c Trajectory and Participant and Clinical Characteristics

Among the groups in each registry, a lower frequency of ethnic minority participants was noted for the trajectories that were low stable and intermediate stable (Table 1). For the high stable group, which is noted to have the most precipitous rise into suboptimal range, minority status was 3-fold higher for the ADDN, 1.3-fold higher for the DPV, and 3.5-fold higher in the T1DX, when comparing with the low stable group in each respective registry ($P \leq .0001$ for minority status differences between groups in each registry). For those in the target increase group, the percentage of minority participants was numerically higher than the low stable and intermediate stable groups. Additionally, those in the high increase group, who had above-target HbA1c levels at baseline with a progressive deterioration in glycemia, were older when assessing the median age at diagnosis across all 3 registries ($P \leq .001$).

DISCUSSION

To our knowledge, our analysis provides the first opportunity to assess unique HbA1c trajectories identified from the time of disease onset and adds to group-based modeling previously applied to longitudinal data in T1D populations.[7,8,21–25] Across all 3 registries, similar trajectory patterns and the proportion of the cohort per trajectory were noted. This is consistent with the assessment of HbA1c over the course of childhood to adolescence in 8 high-income countries, which revealed that, although baseline HbA1c levels varied, the path followed by each cohort was strikingly similar.[6] Hence, our analysis highlights that tracking of HbA1c trends from the time of diagnosis may allow for categorization of those who are most likely to have deterioration in glycemia. Real-world application of such modeling may allow clinicians to provide additional educational interventions, intensification of therapy, and closer follow-up to patients with expected progressive deterioration in glycemia. Furthermore, a deterioration in glycemia despite intensification of therapy may have an underlying biological predisposition and may be associated with future risk of complications.

Prahalad et al[26] previously analyzed HbA1c trajectory using locally weighted scatter plot smoothing techniques (LOESS curves) from the time of diagnosis in a cohort of 261 pediatric participants, noting a deterioration in control after 5-months of disease duration. In that analysis, variables associated with differences between groups in their HbA1c trajectories included age (≤6 vs 6–13 years), those with public insurance instead of private coverage, and those in minority groups, when compared with those who are non-Hispanic white.[26] Similarly, using a larger single-center cohort of 2218 participants managed from 3 months after diagnosis, Clements et al[27] showed those diagnosed with diabetes at an older age had greater glycemic deterioration over time. When grouped by era of diagnosis (defined as pre-2000, 2000–2003, and 2004–2009), those diagnosed with

TABLE 1 Association Between Trajectory Group and Covariates in Each Registry

	Trajectory 1: Green, Low Stable	Trajectory 2: Blue, Intermediate Stable	Trajectory 3: Purple, High Stable	Trajectory 4: Yellow, Target Increase	Trajectory: Red, High Increase	*P*
ADDN ($N = 7292$)						
%	22	44	18	10	6	—
Age at diagnosis, median (IQR), y	8.4 (4.5–12.1)	7.3 (4.1–10.6)	8.0 (4.9–10.7)	9.0 (6.5–11.1)	11.0 (8.9–13.0)	<.001
Male sex, %	55.3	51.8	50.3	48.0	46.9	.003
Adolescent, %[a]	35.9	26.1	28.0	32.5	59.1	<.001
Minority, %	7.2	8.5	12.5	12.5	20.9	<.001
Aggregated HbA1c trajectory in the first year after diagnosis, median (IQR), %[b]	6.6 (6.0–7.1)	7.6 (7.0–8.1)	8.4 (7.8–9.0)	7.1 (6.5–7.6)	8.6 (7.6–9.8)	<.001
DPV ($N = 39226$)						
%	27	43	14	11	5	—
Age at diagnosis, median (IQR), y	8.2 (4.7–11.9)	8.0 (4.7–11.1)	9.9 (6.4–12.2)	9.7 (7.5–11.9)	12.0 (10.3–13.3)	<.001
Male sex, %	55.3	52.5	50.9	51.6	51.2	<.001
Adolescent, %[a]	34.5	29.9	44.7	41.7	71.6	<.001
Minority,%	16.6	19.5	23.9	19.7	22.3	<.001
Aggregated HbA1c trajectory in the first year after diagnosis, median (IQR), %[b]	6.2 (5.8–6.7)	7.0 (6.5–7.5)	8.0 (7.4–8.6)	6.6 (6.1–7.2)	7.9 (7.0–9.1)	<.001
T1DX ($N = 3704$)						
%	27	43	12	12	6	—
Age at diagnosis, median (IQR), y	6.0 (3.0–9.0)	5.0 (3.0–8.0)	5.0 (3.0–9.0)	5.0 (4.0–7.0)	8.0 (6.0–10.0)	<.001
Male sex, %	55.2	51.8	46.2	53.0	48.3	.022
Adolescent, %[a]	19.0	12.2	17.7	6.0	26.3	<.001
Minority, %	11.9	16.9	27.5	24.5	42.9	<.001
Aggregated HbA1c in the first year after diagnosis, median (IQR), %[b]	7.1 (6.5–7.6)	7.8 (7.2–8.5)	8.8 (8.0–9.4)	7.6 (6.9–8.3)	8.3 (7.5–9.4)	<.001

For continuous variables, medians with quartiles are shown. For binary variables, proportion was used. —, not applicable.

[a] Pubertal status was not assessed by tanner staging. Instead, an age threshold of >10 y for women and >11 y for men was employed to estimate the percentage of each cohort that may be considered to be adolescents.

[b] The aggregated HbA1c in the first year after diagnosis represents the aggregated mean HbA1c from 3 mo to 1 y after diagnosis.

diabetes had lower mean HbA1c levels in the 5 years post diagnosis.[27] Yet, when stratified by era, an older age at diagnosis remained associated with greater glycemic deterioration.[27] Finally, Lawes et al[28] previously assessed the HbA1c trajectories in a small cohort ($n = 155$) of youth from the time of diagnosis. However, in all instances, the investigators conducted their analyses using different statistical methods, and group-based modeling was not employed, differentiating our present analysis from previous work.[26–28]

Although a limited number of covariates was available to explore across the 3 registries, a clear picture is evident: those in minority groups have a higher frequency of falling into the trajectory characterized as suboptimal from diagnosis, with a subsequent rise in glycemia. In previous analyses, researchers have documented this same preponderance of minority status in this trajectory pattern.[8,22,27–29] A number of factors likely impact this disparity in glycemia, including racial differences that exist with the mean glucose-HbA1c relationship, which has been shown in a previous study to

account for a 0.4% (4 mmol/mol) higher HbA1c for a given mean sensor glucose level in an African American population, when compared with individuals who are white.[30] This variation may be due, in part, to red cell kinetics.[31] In 2017, an analysis by Beck et al[32] highlighted that HbA1c may over or underestimate mean glucose, when compared with mean sensor glucose data gathered from continuous glucose monitors (CGMs). Thus, the use of CGMs, which measure glucose in interstitial fluid through a subcutaneously placed electrode coated with glucose oxidase, may overcome some of the issues related to HbA1c measurements.

Additionally, structural racism may contribute to lower penetration of technology because of implicit bias of providers, which may impact HbA1c.[33] Indeed, lower rates of pump and sensor use in ethnic minorities have been associated with the glycemic disparities identified.[34–37] The opportunity to transition to such technologies has at times been tied to perceived measures of engagement, including frequency of self-monitoring blood glucose. Importantly, a study by Valenzuela et al[38] explored regimens prescribed for diabetes management among a diverse patient cohort and found that 22% of African American youth endorsed that they were advised to test <3 times a day, a rate that was almost 3-fold higher when compared with white, non-Hispanic and Hispanic youth (8.6% and 7.2%, respectively). Furthermore, the frequency of multiple daily injection use that did not include a basal long-acting analogue dose accounted for a majority of the African American (82.4%) and Hispanic (49.2%) youth groups.[38] More recently, data from the T1DX revealed a lower frequency of diabetes technology use and higher HbA1c levels in those in the lowest socioeconomic status (SES) quintile on the basis of data from 2010 to 2012, with this HbA1c gap being further widened in the T1DX data from 2016 to 2018 .[39] Data from the DPV registry revealed smaller differences in HbA1c on the basis of SES, but this did not appear to be related to technology implementation.[39]

In the present analysis, because data regarding treatment regimen were not collected in all registries, the influence of these technologies on the HbA1c was not able to be explored, yet it is evident that providers need to be cognizant of the potential barriers to device uptake that may lead to underprescribing of such technologies, which may only further the chasm of inequities faced by minority youth. A paradigm shift is needed. By allowing introspection, clinicians can forge a new path with those they care for by forging the concept of the "appropriate candidates" for technology and replacing it with the conviction that all persons with diabetes will benefit from technology. This will lead to discussions of new technologies and therapies during each clinical encounter and, undoubtedly, increase the likelihood of adoption. Furthermore, it is imperative to advocate for equitable access to technology for all persons with diabetes, a factor that becomes even more important as automated insulin delivery systems penetrate clinical care.

To detect trends in glycemic trajectories, the present analysis relied on HbA1c levels; however, with incorporation of CGM into clinical care, it is plausible that analysis could instead be based on time in range metrics, which are anticipated to yield similar trajectories to those identified on the basis of HbA1c. Further highlighting the potential to use this modality are the recent data from the T1DX and DPV registries revealing increased use of CGM, particularly in the pediatric patients[40,41] and the fact that standardized metrics for reporting CGM data and consensus guidelines for the targets for time in range already exist.[42,43] In the present analysis, the high increase trajectory reaches an HbA1c of 9% (75 mmol/mol) within the first 2 years after diagnosis, and the target increase reveals progressive deterioration in glycemia reaching above-target HbA1c levels 3 to 4 years after diagnosis. With HbA1c measurements often tied to in-clinic visits, they are typically obtained quarterly. However, with cloud-based data aggregation from CGM, analytics based on time in range data could be used to identify, in real-time, those needing intensification of therapy. This could trigger follow-up with the clinical team.

With identification of those at greatest risk for glycemic deterioration, resources could specifically be focused on these high-risk groups. Increasing the frequency of follow-up with the clinical team would be essential as well identifying barriers to maintaining and improving glycemia. These more frequent touchpoints may allow for exploration of how to collaboratively develop a plan to optimize therapy, whether through alteration of insulin doses, integration of diabetes management technologies (like pumps and sensors), or engaging caregivers in the oversight of their child's care. With the advent of automated insulin delivery systems, which are composed of a CGM that transmits sensor glucose data to an algorithm that alters insulin delivery administered via an insulin pump, studies have revealed an improvement in time in the target

range, especially in the overnight period, which has been tied to reports of improved sleep.[44] Ensuring youth who are experiencing deterioration in glycemia are provided with information regarding these systems and the opportunity to use them will require lobbying for coverage of these devices for all people with diabetes. This modality of insulin delivery holds the promise of subverting the worsening of glycemia noted in some youth. Reviewing the cornerstones of diabetes management with both the person with diabetes, as well as their family members, could help identify opportunities for reinforcement of key concepts. Additionally, exploring whether diabetes distress, depression or anxiety are present in either the child or the caregivers, is essential. In addition, should any of these issues be identified, referral to a mental health specialist may help subvert ongoing glycemic deterioration.

With the coronavirus disease 2019 pandemic, many clinicians needed to quickly pivot to integrate telehealth options into their care delivery model. By overcoming barriers related to the need to travel to the physical clinic space and alleviating issues regarding the care of siblings as families can take these visits from home, it is possible that telehealth visits may allow for increased engagement of those with deterioration in glycemia. Recent results from a 6-month quasi-randomized trial in which 240 youth either continued usual clinical care or were part of an intensively treated group who received monthly telehealth visits revealed a decreased diabetes burden and increased treatment satisfaction.[45] At the end of the 6-month study period, no difference was appreciated in HbA1c levels; however, those with psychiatric disease and the most suboptimal glycemia (HbA1c level ≥90.0%) showed a trend for greater improvements.[45] Few visits were postponed or missed, suggesting the use of telehealth could help engage youth with deterioration in glycemia.[45] Although provisions for telehealth have been made available during the pandemic to allow for reimbursement and for clinicians in the United States to, potentially, provide care across state lines,[46] how such rules and regulations will change in the postpandemic era remains to be seen.[47] Additionally, because there may be limited numbers of behavioral health specialists in certain geographic regions, the possibility of connecting via telehealth to receive these critical services may alleviate the dearth of mental health providers.[48]

By using the data available from 3 international registries, it is evident that limitations exist. Only a few covariates were collected in a way that allowed for analysis of their relationship to the HbA1c trajectories. Indeed, demographic factors such as BMI, income, educational level, SES, and insurance status were not consistently available, limiting the ability to explore how this may impact trajectories. The same held true for variables that describe current treatment regimen and engagement with that regimen because data were not available in all registries on the mode of insulin delivery, use of CGM, frequency of self-monitoring of blood glucose, and number of boluses per day. Thus, the focus of the present analysis was on sex, minority status, and age at disease onset. Recognizing that minority status does not delve into genetic variations that may underly outcomes regarding incidence of certain disease states, responses to treatment, and disease prognosis, this variable is being used as a surrogate for ancestry because these data were not available for the present analysis.[49] Although minority status was classified differently among the 3 registries, it is important to note that, in the current study, minority status was based on definitions used by each registry and applicable to the respective society.[39,41,50] Yet our findings highlight the same trend for a higher proportion of minority participants being categorized in the trajectory, with suboptimal and progressively deteriorating glycemia across all 3 registries. Although data regarding tanner staging were not routinely collected in the registries, an age-based threshold was used to determine the frequency of youth classified as adolescents. A statistically significant difference in the frequency of adolescents by trajectory as noted across all 3 registries with the proportion of adolescents being largest in the high increase trajectory, a group that was also characterized as having the oldest median age at diagnosis. Clearly, there is the potential for interdependence of these variables and, as a more rigorous method to assess pubertal status was not employed, these results should be interpreted with caution. Finally, although the ADDN and DPV represent true population-based registries, the T1DX encompasses data collected from >80 adult and pediatric diabetes centers. Thus, not all individuals with diabetes living in these regions are part of the cohort nor is the method of data collection consistent among the 3 registries, which may impact the generalizability of our results.

The present analysis also cannot be used to assess whether inherent biological factors contribute to categorization into specific HbA1c trajectories. Because residual β-cell function may impact glycemic

variability and the frequency of complications,[51] identification of those who may retain endogenous insulin production may help a prediction models to determine those at least risk for progressive deterioration of glycemia. Recently, the concept of determining endotypes for those with T1D has been proposed, given the heterogeneity of the condition.[52] This would then provide areas to explore which may include, for example, assessment of whether particular phenotypes and certain autoantibodies are present, as well as the genotype, which may be related to HLA antigen subtype, and may help determine who is at greatest risk for glycemic deterioration. This would then provide the basis for precision medicine, regarding both translational research and clinical care, and exploration of this area is warranted.

CONCLUSIONS

Despite representing data from 3 international registries spanning multiple continents, similar postdiagnostic HbA1c patterns were noted with a striking concordance of 5 distinct HbA1c trajectories identified. Aggregated data from the first year after diagnosis reveals that ∼12% to 18% of registry participants have above-target HbA1c levels that remain stable over time (high stable). Additionally, those with progressive deterioration in glycemia represent a small proportion of all participants studied (∼15%). With one-third of each cohort falling into one of these categories (high stable, target increase, and high increase), the question now becomes how we identify and intensify services to individuals following these patterns. Understanding those with elevations in HbA1c levels into the above target range within the first few years after diagnosis and patient characteristics, such as minority status and a later age at disease onset, may assist in these endeavors. In the age of precision medicine, the ability to project which patients most need services will be critical to ensure quality outcomes are met for all, while minimizing costs.

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ABBREVIATIONS

ADDN: Australasian Diabetes Data Network
CGM: continuous glucose monitor
DPV: Diabetes Patienten Verlaufsdokumentation
HbA1c: hemoglobin A1c
IRB: institutional review board
IQR: interquartile range
SES: socioeconomic status
T1D: type 1 diabetes
T1DX: Type 1 Diabetes Exchange Clinic Registry

Patient-level data are not approved for distribution to outside sources according to the ethical approval at registry sites. Interested researchers can reach out to the individual coordinating center, which may be able to support data analysis requests.

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