ORIGINAL ARTICLE

The SWEET Project 10-Year Benchmarking in 19 Countries Worldwide Is Associated with Improved HbA1c and Increased Use of Diabetes Technology in Youth with Type 1 Diabetes

Peter Gerhardsson, MSc,¹ Anke Schwandt, MSc,^{2,3} Michael Witsch, MD,⁴
Olga Kordonouri, MD, PhD,⁵ Jannet Svensson, MD, PhD,^{6,7} Gun Forsander, MD, PhD,⁸
Tadej Battelino, MD, PhD,⁹ Henk Veeze, MD, PhD,¹⁰ and Thomas Danne, MD,^{5,11}
on Behalf of the SWEET Study Group

Abstract

Objective: The international SWEET registry (NCT04427189) was initiated in 2008 to improve outcomes in pediatric diabetes. A 10-year follow-up allowed studying time trends of key quality indicators in 22 centers from Europe, Australia, Canada, and India in youth with type 1 diabetes (T1D).

Methods: Aggregated data per person with T1D <25 years of age were compared between 2008–2010 and 2016–2018. Hierarchic linear and logistic regression models were applied. Models were adjusted for gender, age-, and diabetes duration groups.

Results: The first and second time periods included 4930 versus 13,654 persons, 51% versus 52% male, median age 11.3 [Q1; Q3: 7.9; 14.5] versus 13.3 [9.7; 16.4] years, and T1D duration 2.9 [0.8; 6.4] versus 4.2 [1.4; 7.7] years. The adjusted hemoglobin A1C (HbA1c) improved from 68 (95% confidence interval [CI]: 66–70) to 63 (60; 65) mmol/mol ($P < 0.0001$) or 8.4 (95% CI: 8.2–8.6) to 7.9 (7.6; 8.1) % ($P < 0.0001$). Across all age groups, HbA1c was significantly lower in pump and sensor users. Severe hypoglycemia declined from 3.8% (2.9; 5.0) to 2.4% (1.9; 3.1) ($P < 0.0001$), whereas diabetic ketoacidosis events increased significantly with injection therapy only. Body mass index-standard deviation score also showed significant improvements 0.55 (0.46; 0.64) versus 0.42 (0.33; 0.51) ($P < 0.0001$). Over time, the increase in pump use from 34% to 44% preceded the increase in HbA1c target achievement (<53 mmol/mol) from 21% to 34%.

Conclusions: Twice yearly benchmarking within the SWEET registry was associated with significantly improved HbA1c on a background of increasing pump and sensor use for 10 years in young persons with T1D.

Trial Registration: NCT04427189.

¹Department of Epidemiology, Institute of Applied Economics and Health Research, Copenhagen, Denmark.

²Institute of Epidemiology and Medical Biometry, ZIBMT, Ulm University, Ulm, Germany.

³German Center for Diabetes Research (DZD), Munich-Neuherberg, Germany.

⁴Department of Pediatrics DCCP, Center Hospitalier de Luxembourg, Luxembourg, Luxembourg.

⁵Children's Hospital AUF DER BULT, Hannover Medical School, Hannover, Germany.

⁶Department of Pediatrics and Adolescents, Copenhagen University Hospital, Herlev and Gentofte, Herlev, Denmark.

⁷Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark.

⁸Department of Pediatrics, Institute for Clinical Sciences, Sahlgrenska Academy, University of Gothenburg and Region Västra Götaland, Sahlgrenska University Hospital, Queen Silvia Children's Hospital, Gothenburg, Sweden.

⁹UMC-University Children's Hospital and Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia.

¹⁰Diabeter, Diabetes Center for Pediatric and Adolescent Diabetes Care and Research, Rotterdam, Netherlands.

¹¹SWEET e.V., Hannoversche Kinderheilstalt, Hannover, Germany.

Keywords: Type-1 diabetes, Hemoglobin A1c, Benchmarking, Insulin pumps, Continuous glucose monitoring, Hypoglycemia, Diabetic ketoacidosis; the SWEET project, Diabetes registry, Glycemic control.

Background

GLYCATED HEMOGLOBIN A1C (HbA1c) predicts the future complication rate for children and adolescents diagnosed with type 1 diabetes (T1D).^{1–3} HbA1c is the most widely studied quality indicator,^{4–7} but several other factors are important for cardiovascular health, such as body mass index (BMI), lipids, and blood pressure^{8–10}; additionally, experiencing severe hypoglycemia, long-term hyperglycemia, or diabetic ketoacidosis (DKA) might have cognitive consequences.^{11,12}

Benchmarking has a long tradition in pediatric diabetology.^{4,6,7,10} The comparison of quality indicators among different centers or countries is proven to be effective in some registries.^{6,7} An observational study reporting quality indicator without comparing results among centers had little or no impact.⁵ Many studies have tried to explain differences among centers by comparing treatment strategies,^{6,13–15} but treatment target setting proved the most impactful.^{16,17} In addition, the relationship between quality of life and glycemic control is well established.¹⁸ However, the reasons why benchmarking is successful in some environments and not in others remain elusive, and whether changing the treatment target leads to improved glycemia remains speculative.

During the past 10 years, centers worldwide have implemented treatment with modern technology including insulin pumps and continuous glucose monitoring (CGM) in children with T1D.^{19,20} Most research studies using these technologies are associated with improved glycemic control; real-life observations may not necessarily show the same.²¹

The SWEET project (Better Control in Pediatric and Adolescent Diabetes: Working to Create Centers of Reference) was established in 2008 as a 3-year EU Public Health Program. The purpose was to harmonize care of children with T1D through establishing “centers of reference” (CoR) in European countries.²² The pursuit is not to acclaim centers of excellence, but to identify the actual background that makes them excel. On the basis of reliable collection of high-quality data displayed in standardized benchmarking reports, participants aim to understand how some centers achieve better outcomes than those with similar resources, to learn from one other, and to advance the culture of shared knowledge. Factors responsible for variations may include frequent uploads of pump or CGM data, individual targets, targeted education programs, or assessment of patient-reported outcome measures included into daily practice.⁴ Beginning in 2011, SWEET e.V. became registered as a nonprofit charity and has developed into a worldwide initiative under the auspices of the International Society for Pediatric and Adolescent Diabetes (ISPAD). The focus has changed from establishing and accrediting CoR for pediatric and adolescent diabetes to that of collaboration and inclusion among smaller centers to support database development and quality improvement in high-, medium-, and low-income countries.

The aim of this study was to analyze the selected quality indicators from the initial SWEET database over the past decade and study the impact of treatment changes.

Research Design and Methods

Data sources and subjects

This analysis was based on data from the international prospective multicenter diabetes registry SWEET. SWEET (NCT04427189) was approved by the ethical committee of Hannover Medical School and is associated with the AUF DER BULT Diabetes Center for Children and Adolescents, Hannover, Germany, which coordinates the SWEET collaboration. Each center has to meet specific entry criteria showing diabetes expertise and compliance with the ISPAD clinical practice guidelines. The local institutional review boards of the participating centers approved the pseudonymized data collection (for details please refer to the website www.sweet-project.org).

The SWEET database combines data from distinct sources.^{10,23} Data are collected locally through clinical databases, electronic health record systems, the standardized SWEET-DPV-documentation software (<https://sweet.zibmt.uni-ulm.de/software.php>), or centers download data from existing longitudinal registries. Twice yearly, data are transmitted to the central database hosted by the Institute of Epidemiology and Medical Biometry, ZIBMT, Ulm University, Ulm, Germany. The prospectively collected data are then combined into a common database. Inconsistent/improbable or missing data are reported back to the centers for correction. To meet the General Data Protection Regulation, data are then aggregated into an anonymized cumulative database used for clinical research, scientific analysis, and international benchmarking. All centers are peer reviewed, and on this basis we estimate that the great majority of patients treated at a center are in the database. However, on a center level we are not certain about the absolute completeness for each year. The intention of this study is not to delineate individual center performance; therefore, center-specific data are not identified.

As of September 2019, the SWEET database includes 66,418 participants and 724,724 visits documented by 101 diabetes centers worldwide. The growth of SWEET has occurred since the creation of the charity and willing participation at a cost to centers. However, when this present analysis was done, the criteria for inclusion were centers with data from at least 15 individuals with documented HbA1c per center, individuals with T1D aged ≤ 25 years during the first time period (2008–2010) and the second time period (2016–2018). As SWEET started as an EU project, these centers came primarily from Europe (Austria, Czech Republic, Denmark, France, Germany, Greece, Hungary, Ireland, Italy, Luxembourg, Poland, Portugal, Romania, Serbia, Sweden, and Turkey) and included centers from Australia, Canada, and India. Data from eligible children and youth with T1D from participating centers were aggregated for each subject during the observation periods. A subanalysis was performed in subjects with data documented in both time periods.

Outcome variables

Glycemic control was assessed by HbA1c measured locally in each center. To adjust for differences between

laboratories, the multiple of the mean method was used to standardize local HbA1c mathematically.¹⁰ Insulin therapy was classified as pump therapy or injection therapy. Frequency of self-monitoring of blood glucose (SMBG) was recorded per day. Any use of CGM (real-time or intermittent scanning CGM) was analyzed.

To adjust for age and gender, BMI and height standard deviation score (SDS) values were calculated using the international pediatric reference data from the World Health Organization (WHO) (www.who.int/childgrowth/standards/bmi_for_age/en/). Frequency of severe hypoglycemia and DKA, both defined based on the ISPAD 2018 guidelines, were further analyzed. Severe hypoglycemia was defined as an event during which a person with diabetes requires assistance of another person to administer carbohydrates, intravenous glucose, or glucagon, and diabetes ketoacidosis was defined as pH <7.3 or serum bicarbonate <15 mmol/L. Lipids including total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol were measured locally using standardized automated instrumentations.²⁴ Systolic and diastolic blood pressure SDS values were calculated based on fourth report references.²⁵ Age and duration of T1D were grouped to achieve comparable group sizes (age: ≤6 years, >6 to ≤12 years, >12 to ≤16 years, and >16–25 years; and T1D duration: ≤2 years, >2 to ≤5 years, >5–7 years, and >7 years).

Statistical analysis

Descriptive data are presented as median with quartiles or percentages. The Wilcoxon test was used to compare continuous variables and the chi-squared test was used for binary variables.

Linear and logistic regression models were applied to adjust for covariates. To account for variation among diabetes centers, each center was entered as a random intercept in the models. To adjust for multiple comparisons, Tukey–Kramer test was used. Regression models were adjusted for age, gender, and diabetes duration. Results are presented as adjusted means with 95% confidence intervals (CIs).

Curves of aggregated HbA1c values per year of age were estimated in the entire cohort across both time points using locally weighted scatter plot smoothing (LOESS).²⁶

In the subanalysis of individuals with data in both time periods, linear regression model for HbA1c was applied. Repeated measurements per subject were taken into account using first-order autoregressive covariance structure. Models were adjusted for gender, age groups as above (missing the youngest age group), and diabetes duration groups. Regression models were additionally adjusted for pump usage and sensor usage. A two-sided *P*-value <0.05 was defined as statistically significant. All analyses were performed with Statistical Analysis Software 9.4 (SAS; SAS Institute, Inc., Cary, North Carolina).

Results

A total of 22 centers from 19 countries in Asia (India), Australia, Europe (Czech Republic, Denmark, France, Germany, Greece, Hungary, Ireland, Italy, Luxembourg, Poland, Portugal, Romania, Serbia, Sweden, and Turkey), and North America (Canada) had at least 15 eligible subjects in each

observation period. In this study, 16,082 children and youth with T1D from 22 centers were included. The cohort from the first observation period (2008–2010) included 4930 persons from 22 centers, 51% male, median age 11.3 years [Q1; Q3: 7.9; 14.5], and median T1D duration 2.9 years [0.8; 6.4]. The second time cohort (2016–2018) included 13,654 persons, 52% male, age 13.3 years [9.7; 16.4], and diabetes duration 4.2 years [1.4; 7.7]. A subanalysis was performed in 2502 subjects with data documented in both time periods.

Glycemic control in the entire cohort

The unadjusted mean HbA1c for the first time period was 62 [55; 72] mmol/mol or 7.8 [7.2; 8.7] % and 58 [51; 68] mmol/mol or 7.5 [6.8; 8.4] % for the second time period. LOESS curves revealed that this improvement was present in all age groups (Fig. 1). This difference remained significant when adjusted for gender, age, and T1D duration. Adjusted HbA1c for the first time period was 68 (95% CI: 64–72) mmol/mol or 8.4 (95% CI: 8.0–8.7) %, and 63 (60; 67) mmol/mol or 7.9 (7.6; 8.3) % for the second time period (*P* < 0.0001) (Fig. 2A).

Clinical outcomes in the entire cohort

Clinical variables were analyzed in the entire cohort adjusted for gender, age, and T1D duration (Table 1). The use of insulin pumps and sensors increased from 2008–2010 to 2016–2018 significantly. Adjusted HbA1c improved significantly in all age groups, in those treated with pumps or injection therapy. However, lower HbA1c values were achieved at both time points in those on CSII in all age groups (Table 1). Despite the dramatic increase of sensor use, the number of SMBG strips per day increased also minimally between the time points. Frequency of severe hypoglycemia was significantly reduced between the two time periods from 3.8% (2.9; 4.9) to 2.4% (1.9; 3.1) (*P* < 0.0001). A doubling in the DKA rate was seen in those using injection therapy, whereas no significant difference between both time points was observed in pumps (Table 1).

The improvement of HbA1c over the 10-year period was accompanied with significant improvements in some other risk factors for cardiovascular disease such as BMI-SDS, systolic BP-SDS, and total cholesterol. However, after additional adjustment for HbA1c, cholesterol decrease was no longer significant (165 [161; 169] vs. 164 [161; 168] mmol/L).

Subcohort of subjects with HbA1c values at both time points

Most centers experienced a considerable increase in number of patients reported in the registry over the course of 10 years. Thus, an additional comparison of the 2008–2010 cohort with the 2016–2018 cohort was done by analyzing the 2502 persons with T1D who had HbA1c values available in both time periods. Again, after adjustment for age, gender, and diabetes duration, a decline was seen between the two time periods (Fig. 2B). When analyzing the age groups, <12, 12–16, and 16–25 years of age, the HbA1c values were reduced in the two youngest cohorts, 64 (63; 65) to 58 (57; 61) mmol/mol or 8.0 (7.9; 8.1) to 7.5 (7.4; 7.7) % in the group <12 years of age, and 68 (66; 70) to 63 (62; 64)

FIG. 1. Curves of HbA1c per age for the entire cohort were estimated using locally weighted scatter plot smoothing (LOESS, shaded area: LOESS fit +95% CI) by age (years) 2008–10 (blue triangle) $n=4,930$ and 2016–2018 (green circle) $n=13,654$ with circles/triangles indicating the HbA1c for each year of age in each time period. There is no overlap of the CI indicating significant differences in all age groups. CI, confidence interval; HbA1c, hemoglobin A1C. Color images are available online.

mmol/mol or 8.4 (8.2; 8.6) to 7.9 (7.8; 8.0) % in the group 12–16 years of age. In the older age group 16–25 years of age, there was no significant change in HbA1c (65 [58; 70] vs. 65 [64; 66] mmol/mol) or (8.1 [7.5; 8.6] vs. 8.1 [8.0; 8.2] %). As in the total cohort, pump users had lower HbA1c values in both time periods (63 [62; 65] to 60 [58; 61] mmol/mol [$P<0.001$] or (7.9 [7.8; 8.1] to 7.6 [7.5; 7.7] % [$P<0.001$]) compared with those on injections (69 [67; 70] to 64 [63; 65] mmol/mol [$P<0.0001$] or 8.0 [8.3; 8.6] to 8.0 [7.9; 8.1] % [$P<0.001$]).

Changes of glycemic control on a center level

To analyze the changes in glycemic control on a center level, HbA1c values were aggregated per center in each time period. Although the magnitude of improvement varied considerably, and for many centers it was $<0.5\%$, usually considered as clinically significant, only one center deteriorated in average HbA1c over the 10-year period and improvements were seen independent of baseline glycemic control (Fig. 3). We found no evidence for the change of

FIG. 2. Adjusted comparison of glycemic control between the two time periods 2008–2010 and 2016–2018. Results are presented as adjusted means with 95% CIs. (A) Entire cohort: Linear regression model was used adjusted for gender, T1D duration, and age. Center was entered as a random intercept in the models. (B) Cohort of patients with data available at both time points: Analyzing the subcohort of individuals with data in both time points, repeated measurements per subject were taken into account in the regression models. The line indicates the average decline during this time and the error bars reflect the 95% CI. Both comparisons, (A, B) are significant $P<0.001$. T1D, type 1 diabetes.

TABLE 1. ADJUSTED COMPARISON OF CLINICAL OUTCOMES BETWEEN THE TWO TIME PERIODS

	<i>Time period 1 (2008–2010)</i>	<i>Time period 2 (2016–2018)</i>	<i>P</i>
Clinical variables			
BMI-SDS	0.55 (0.46; 0.64)	0.42 (0.33; 0.51)	<0.0001
Diastolic blood pressure-SDS	0.13 (0.06; 0.20)	0.28 (0.21; 0.35)	<0.0001
Systolic blood pressure-SDS	0.20 (0.09; 0.30)	0.19 (0.08; 0.29)	0.59
DKA, %	2.3 (1.6; 3.2)	3.8 (2.8; 5.0)	<0.0001
Pump users, %	2.6 (1.7; 4.1)	3.4 (1.7; 4.0)	0.16
MDI users, %	2.2 (1.4; 3.3)	4.0 (2.9; 5.6)	0.0001
Severe hypoglycemia events, %	3.7 (2.9; 4.9)	2.4 (1.9; 3.1)	<0.0001
Pump users, %	6.2 (4.6; 8.4)	2.6 (2.0; 3.2)	<0.0001
MDI users, %	4.9 (3.6; 6.7)	2.4 (1.8; 3.2)	<0.0001
Total cholesterol, mg/dL	167 (164; 171)	166 (163; 168)	0.03
Total cholesterol, mmol/L	9.3 (9.1; 9.4)	9.2 (9.0; 9.3)	
HDL, mg/dL	58 (57; 59)	58 (57; 60)	0.43
HDL, mmol/L	3.2 (3.1; 3.3)	3.2 (3.2; 3.3)	
LDL, mg/dL	93 (90; 95)	92 (89; 94)	0.16
LDL, mmol/L	5.2 (5.0; 5.3)	5.1 (5.0; 5.2)	
Therapy			
Pump usage, %	25.7 (21.2; 30.7)	41.8 (36.2; 47.6)	<0.0001
Sensor usage, %	1.5 (1.0; 2.3)	44.6 (2.3; 52.4)	<0.0001
SMBG, per day	4.6 (4.2; 4.9)	4.7 (4.4; 5.1)	0.001
HbA1c (mmol/mol), (%) by age and therapy			
Age <6 years			
Pump	59 (56; 62), 8.6 (7.3; 7.8)	56 (53; 58), 7.3 (7.0; 7.5)	0.0024
MDI	66 (61; 70), 8.2 (7.7; 8.6)	60 (56; 65), 7.6 (7.3; 8.1)	0.0003
Age >6 to ≤12 years			
Pump	61 (56; 66), 7.7 (7.3; 8.2)	58 (53; 63), 7.5 (7.0; 7.9)	<0.0001
MDI	66 (61; 70), 8.2 (7.7; 8.6)	62 (57; 66), 7.8 (7.4; 8.2)	<0.0001
Age >12 to ≤16 years			
Pump	63 (60; 66), 7.9 (7.6; 8.2)	61 (58; 63), 7.7 (7.5; 7.9)	0.0144
MDI	70 (65; 75), 8.6 (8.1; 9)	66 (61; 71), 8.2 (7.7; 8.7)	0.0013
Age >16 years			
Pump	65 (61; 69), 8.1 (7.7; 8.5)	61 (59; 64), 7.7 (7.6; 8.0)	0.0272
MDI	72 (67; 76), 8.7 (8.3; 9.1)	67 (63; 71), 8.3 (7.9; 8.7)	0.0045

Linear and logistic regression model was used adjusted for gender, T1D duration, and age. Center was entered as a random intercept in the models. Results are presented as adjusted means with 95% CIs. DKA and severe hypoglycemia events are measured as incidence during treatment and not at diagnosis.

BMI-SDS, body mass index-standard deviation score; CI, confidence interval; DKA, diabetic ketoacidosis; HbA1c, hemoglobin A1C; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MDI, multiple daily injections; SMBG, self-monitoring of blood glucose; T1D, type 1 diabetes.

HbA1c being related to increased number of patients treated per center. The comparison of 9 centers with a significant improvement of HbA1c with 13 centers with less improvement indicated that 8 of 9 versus 6 of 13 had increased their overall number of patients to >200 in the observation period. In particular, the one center with the largest improvement over time belonged to the group with the largest increase in the number of patients, unchanged increase in pump percentage, and increased relative CGM use.

Temporal trends on glycemic target achievement and diabetes technology usage

To investigate the temporal relationship between the use of pumps and sensors and achievement of target HbA1c, data of the entire cohort were aggregated for each year of treatment from 2008 to 2018. Although 21% of the participants achieved a target HbA1c of <7% (53 mmol/mol) in 2008, this remained stable until 2013 when 25% of the participants

achieved this target, with the percentage continuously rising to 34% in 2018. This increase in target achievement was preceded by a rise in pump use from 34% to 44% in 2013, when it plateaued until 2018. In contrast, sensor use was negligible until the year 2015 with a sharp rise thereafter, so that more than half of the participants had a sensor in 2018 (Fig. 4).

Discussion

Our analysis demonstrated a sustained improvement in metabolic outcomes within the SWEET international network of CoR for pediatric diabetes in its first 10 years. The SWEET mission to harmonize care and to improve outcomes for children with diabetes based on agreed standards of care following international guidelines, quality control including peer audits for center certification, and data collection with biannual standardized benchmarking reports and exchange of best practices during the annual meetings^{14,21–23} seems to progress in the right direction. Significant differences exist in

FIG. 3. HbA1c data aggregated per center for each time period and the regression line +95% CI (shaded region). All centers below the angle bisector have shown an improvement in average A1c between the two time periods. However, the average improvement of $\geq 0.5\%$ HbA1c was achieved only in 9 out of 22 centers.

access to modern treatment regimens within countries and centers participating in SWEET,²⁷ but it is encouraging that most centers were able to improve nonetheless.

Over the past 10 years, nearly all SWEET centers showed an improvement in average HbA1c across all age groups, with an increased percentage of children and adolescents achieving the current ISPAD glycemic target (<53 mmol/mol or $<7\%$)³ even though the standard target during the study period was higher (<58 mmol/mol or $<7.5\%$). Improvement in quality indicators of lower BMI, and lower cholesterol levels were demonstrated. Although improved cholesterol levels could be explained by improved glycemic control, there was an independent effect of BMI after adjustment. These improvements were possibly associated with increased

use of diabetes technology: an increase in insulin pump use preceded the increased proportion of children and adolescents achieving the target HbA1c. Similar improvements are reported also by some but not all national pediatric registries.^{5-7,19} As these outcomes are not limited to HbA1c but also include common cardiovascular risk factors, they could possibly be associated with less cardiovascular mortality in the future. As the increased cardiovascular risk in T1D is related to earlier diabetes onset,² our results advocate the use of diabetes technology in the pediatric population. Moreover, there are several reports that COVID-19 has led to increased use of diabetes technology for telemedicine in pediatric diabetes care in many centers. Thus, the use of technology allows target-driven pediatric diabetes care also under the

FIG. 4. Temporal patterns of CSII and CGM use in centers and HbA1c. HbA1c data of the entire cohort were aggregated for each year of treatment from 2008 to 2018. CGM, continuous glucose monitoring.

conditions of a virtual diabetes clinic.²⁸ An overall reduction of hyperglycemia with diabetes technology may improve daily cognitive functioning,²⁹ and prevent long-term damage to the developing brain.¹²

Although our analysis confirms other registry data that the effect of age and gender on HbA1c is remarkably similar across countries,³⁰ it shows for the first time that the improved mean HbA1c for the entire population distributes uniformly across all age groups preserving the rise during adolescence, with injections or insulin pumps usage. However, outcomes remained better in pump users across all time points and age groups.

Although observational data cannot prove causality, the longitudinal 10-year SWEET data analysis provides evidence that increased use of diabetes technology in pediatric diabetes centers around the globe is safe and effective. Although infusion set failure could increase the risk for DKA, a significant rise in the DKA rate was only seen in those on injection therapy. It remains to be elucidated whether the reduction of the DKA rates with pump use relates to the selection of individuals for pump therapy, better education, or other factors.²⁰

Our results are different from those from the T1D Exchange registry: although increasing use of CGM is also associated with improved glycemic outcomes, the total T1D Exchange registry cohort showed deteriorating glycemic control.⁵ However, neither the T1D Exchange registry nor SWEET is necessarily representative of the centers, and differences in the completeness of data or rates of loss to follow-up may have contributed to this. T1D Exchange registry did not intend to submit data on all the patients who receive care at those centers; that is, they included a sample of individuals who agreed to participate and were recruited within a specified period of time. By contrast, most pediatric patients who receive care at SWEET participating centers are supposed to be included in the SWEET data collection. Also, the T1D Exchange did not perform benchmarking or peer audit, further limiting the comparability. In the SWEET group, centers are not remunerated for entering their data but rather have to pay an annual membership fee to be part of the charity running the organization. In turn, centers receive peer audit to verify the quality of data collection and health care delivery, as well as standardized biannual benchmarking reports against their peers, aiming at including the total population of youth with T1D at centers.

Although our results are encouraging, most of the young individuals with T1D still remain above the recommended HbA1c target.³ SWEET will perhaps decide for open/public benchmarking, and together with ISPAD adopts and further develops new technology-based diabetes management strategies and targets³¹ for all participating centers to foster additional improvements in glycemic control. The use of technology, with the potential to lower the risk of hypoglycemia, and HbA1c may allow for more stringent CGM-based targets.³²

The observed significant decrease in the BMI-SDS seems to be of particular importance, as it is contrary to several reports from pediatric populations,⁹ and is not associated with HbA1c.⁸

Our study has several limitations: first the two compared periods have vast differences in populations; however, the smaller longitudinal analysis with the same population confirmed our results. Second, the data are center reported from

different countries with unequal methods for data collection; however, the final database was verified biannually and the data were reverified and cleaned. As participation in SWEET is limited to larger centers with multidisciplinary care and fulfilling the criteria of being “centers of reference” put forward by SWEET,²¹ the participating centers cannot be considered representative for a country or region. The countries and sites have different socioeconomic status, insurance, and support for patients that were beyond the scope of this analysis. Unfortunately, the database does not include sufficient data on the severity of DKA or the administration of extra carbohydrates for incipient hypoglycemia to further elucidate the relationship between diabetes technology and acute complications. Despite the stringent analysis plan, it was impossible to completely exclude confounding factors as can be seen in the adjustment effects between HbA1c and cholesterol levels, or to establish causality between participation in SWEET and improvement in outcomes with this real-world data.

Conclusions

Our analysis of the SWEET database demonstrates a sustained improvement in HbA1c over the 10-year period, evenly distributed throughout all pediatric age groups, and possibly associated with the use of diabetes technology, the use of a unified electronic data reporting, benchmarking, peer review, and the SWEET quality improvement strategies. Alternatively, these effects could also be the result of a secular trend and/or the result of other factors as intensification of diabetes management (education, psychosocial support, and technology usage) that have gradually become more widespread around the world. Further strategic developments in diabetes education and management, harmonized care, and unified treatment targets are necessary to prevent diabetes complications and prolong life in the majority of individuals with childhood-onset T1D.

Acknowledgments

We thank the following for their support of this study: Katharina Fink for the data management as well as Andreas Hungele and Ramona Ranz for the DPV software (all Ulm University, Germany), Ines Hiller, Katharina Klee (Kinderkrankenhaus Auf der Bult, Hannover, Germany), and Reinhard Holl (Ulm University, Germany) for their invaluable support and Claudia Graham for an independent review of the content and grammar of the article. Finally, we thank all participating centers of the SWEET network, especially the collaboration centers in this investigation (Supplementary Appendix S1).

Authors' Contributions

P.G., A.S., M.W., O.K., J.S., G.F., T.B., H.V., and T.D. contributed to the study concept and design. P.G., A.S., and T.D. supervised the study. A.S. analyzed the data. All authors participated in data interpretation. Each author drafted a section of the article, the final article was reviewed and approved by all. T.D. is the guarantor of the study and takes full responsibility for the work as a whole, including the study design, access to data, and the decision to submit and publish the article.

Author Disclosure Statement

P.G. is a shareholder of the Inst. of Applied Economics and Health Research. O.K. received honoraria for being on the advisory board of Novo Nordisk as well as speaker's honoraria from Eli Lilly and Sanofi. T.B. served on advisory boards of Novo Nordisk, Sanofi, Eli Lilly, Boehringer, Medtronic, and Bayer Health Care. T.B.'s institution received research grant support, with receipt of travel and accommodation expenses in some cases, from Abbott, Medtronic, Novo Nordisk, GluSense, Sanofi, Sandoz and Diamyd. T.D. has received speaker's honoraria and research support from and has consulted for Abbott, AstraZeneca, Boehringer, DexCom, Lilly, Medtronic, Novo Nordisk, Roche, Sanofi, and Ypsomed. T.D., O.K., and T.B. are shareholders of DreaMed Ltd. P.G., A.S., M.W., J.S., G.F., and H.V. declare that there is no duality of interest associated with their contribution to this article

Funding Information

SWEET is a registered nonprofit charity in Hannover, Germany. It is financed through membership fees of the participating centers (based on income of country of residence according to the World Bank) and corporate members. We acknowledge with gratitude the support from the following SWEET e.V. corporate members—in alphabetical order: Abbott, Boehringer Ingelheim, DexCom Inc., Insulet, Eli Lilly & Co., Medtronic Europe, Sanofi.

Supplementary Material

Supplementary Appendix S1

References

- White NH, Cleary PA, Dahms W, et al.: Beneficial effects of intensive therapy of diabetes during adolescence: outcomes after the conclusion of the Diabetes Control and Complications Trial (DCCT). *J Pediatr* 2001;139:804–812.
- Rawshani A, Sattar N, Franzén S, et al.: Excess mortality and cardiovascular disease in young adults with type 1 diabetes in relation to age at onset: a nationwide, register-based cohort study. *Lancet* 2018;392:477–486.
- DiMeglio LA, Acerini CL, Codner E, et al.: ISPAD Clinical Practice Consensus Guidelines 2018: glycemic control targets and glucose monitoring for children, adolescents, and young adults with diabetes. *Pediatr Diabetes* 2018; Suppl 27:105–114.
- Witsch M, Kosteria I, Kordonouri O, et al.: Possibilities and challenges of a large international benchmarking in pediatric diabetology—the SWEET experience. *Pediatr Diabetes* 2016;17:7–15.
- Foster NC, Beck RW, Miller KM, et al.: State of type 1 diabetes management and outcomes from the T1D exchange in 2016–2018. *Diabetes Technol Ther* 2019;21:66–72.
- Svensson J, Johannesen J, Mortensen HB, Nordly S, on behalf of The Danish Childhood Diabetes Registry: Improved metabolic outcome in a Danish diabetic pediatric population aged 0–18 yr: results from a nationwide continuous Registration. *Pediatr Diabetes* 2009;10:461–467.
- McKnight JA, Wild SH, Lamb MJE, et al.: Glycemic control of Type 1 diabetes in clinical practice early in the 21st century: an international comparison. *Diabet Med* 2015;32:1036–1050.
- Southern RH, Mittelman SD, Wee CP, et al.: A longitudinal assessment of lipids in youth with type 1 diabetes. *Pediatr Diabetes* 2011;12:365–371.
- Åkesson K, Hanberger L, Samuelsson U: The influence of age, gender, insulin dose, BMI, and blood pressure on metabolic control in young patients with type 1 diabetes: influences on HbA1c in type 1 diabetes patients. *Pediatr Diabetes* 2015;16:581–586.
- Maffei C, Birkebaek NH, Konstantinova M, et al.; SWEET Study Group. Prevalence of underweight, overweight, and obesity in children and adolescents with type 1 diabetes: data from the international SWEET registry. *Pediatr Diabetes* 2018;19:1211–1220.
- Cameron FJ, Skinner TC, De Beaufort CE, et al.: Are family factors universally related to metabolic outcomes in adolescents with Type 1 diabetes? *Diabet Med* 2008;25:463–468.
- Fox LA, Hershey T, Mauras N, et al.: Persistence of abnormalities in white matter in children with type 1 diabetes. *Diabetologia* 2018;61:1538–1547.
- Swift P, Skinner T, De Beaufort C, et al.: Target setting in intensive insulin management is associated with metabolic control: the Hvidoere Childhood Diabetes Study Group Center Differences Study 2005. *Pediatr Diabetes* 2009;11:271–278.
- Danne T, Lion S, Madacz L, et al.: Criteria for Centers of Reference for pediatric diabetes—a European perspective. *Pediatr Diabetes* 2012;13 Suppl 16:62–75.
- Hofer SE, Raile K, Fröhlich-Reiterer E, et al.: Tracking of metabolic control from childhood to young adulthood in type 1 diabetes. *J Pediatr* 2014;165:956–961.e1–e2.
- Kordonouri O, Hartmann R, Danne T: Treatment of type 1 diabetes in children and adolescents using modern insulin pumps. *Diabetes Res Clin Pract* 2011;93:S118–S124.
- Van Looke M, Battelino T, Tittel SR, et al.; SWEET study group. Lower HbA1c targets are associated with better metabolic control. *Eur J Pediatr* 2021;DOI: 10.1007/s00431-020-03891-2.
- Hoey H, Aanstoot H-J, Chiarelli F, et al.: Good metabolic control is associated with better quality of life in 2,101 adolescents with type 1 diabetes. *Diabetes Care* 2001;24:1923–1928.
- Dovc K, Telic SS, Lusa L, et al.: Improved metabolic control in pediatric patients with type 1 diabetes: a nationwide prospective 12-year time trends analysis. *Diabetes Technol Ther* 2014;16:33–40.
- Blackman SM, Raghinaru D, Adi S, et al.: Insulin pump use in young children in the T1D Exchange clinic registry is associated with lower hemoglobin A1c levels than injection therapy. *Pediatr Diabetes* 2014;15:564–572.
- Karges B, Schwandt A, Heidtmann B, et al.: Association of insulin pump therapy vs insulin injection therapy with severe hypoglycemia, ketoacidosis, and glycemic control among children, adolescents, and young adults with type 1 diabetes. *JAMA* 2017;318:1358–1366.
- Danne T, Hanas R: The mission of SWEET: harmonize care to optimize outcomes of children with diabetes worldwide. *Pediatr Diabetes* 2016;17 Suppl 23:3–6.
- Piccini B, Schwandt A, Jefferies C, et al.; SWEET registry: Association of diabetic ketoacidosis and HbA1c at onset with year-three HbA1c in children and adolescents with type 1 diabetes: data from the international SWEET registry. *Pediatr Diabetes* 2020;21:339–348.

24. Kosteria I, Schwandt A, Davis E, et al.: SWEET study group: lipid profile is associated with treatment regimen in a large cohort of children and adolescents with type 1 diabetes mellitus: a study from the international SWEET database. *Diabet Med* 2019;36:1294–1303.
25. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents: The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics* 2004;114:555–576.
26. Hermann J, Miller KM, Hofer SE, et al.: The transatlantic HbA1c gap: differences in glycemic control across the lifespan between people included in the US T1D Exchange Registry and those included in the German/Austrian DPV registry. *Diabet Med* 2020;37:848–855.
27. Sumnik Z, Szypowska A, Iotova V, et al.: SWEET study group: Persistent heterogeneity in diabetes technology reimbursement for children with type 1 diabetes: the SWEET perspective. *Pediatr Diabetes* 2019;20:434–443.
28. Danne T, Limbert C: COVID-19, type 1 diabetes, and technology: why pediatric patients are leading the way. *Lancet Diabetes Endocrinol* 2020;8:465–467.
29. Suput Omladic J, Slana Ozimic A, Vovk A, et al.: Acute hyperglycemia and spatial working memory in adolescents with type 1 diabetes. *Diabetes Care* 2020;43:1941–1944.
30. Anderzén J, Hermann JM, Samuelsson U, et al.: International benchmarking in type 1 diabetes: large difference in childhood HbA1c between eight high-income countries but similar rise during adolescence-A quality registry study. *Pediatr Diabetes* 2020;21:621–627.
31. Battelino T, Danne T, Bergenstal RM, et al.: Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. *Diabetes Care* 2019;42:1593–1603.
32. Hanas R, Birkebaek NH, Carlsson A, et al.: No evidence for a change of the current HbA1c target level of $\leq 6.5\%$ (48 mmol/mol) in children and adolescents with diabetes in Sweden and UK. *BMJ* 2019;366:14894.

Address correspondence to:

Peter Gerhardsson, MSc

Department of Epidemiology

Institute of Applied Economics and Health

Research (ApHER)

Ewaldsgade 3

Copenhagen 2200

Denmark

E-mail: peter.gerhardsson@appliedeconomics.dk