Continuous glucose monitoring use and glucose variability in very young children with type 1 diabetes (VibRate): A multinational prospective observational real-world cohort study

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1 | INTRODUCTION

Precise management of type 1 diabetes (T1D) is challenging. For very young children and their families, diabetes care is further complicated daily by unique challenges associated with this developmental period, including unpredictable eating patterns and a high degree of variability in day-to-day insulin requirements.1 There is increasing evidence that both glycaemic excursions early in the disease course and high glucose concentrations have detrimental effects on the developing brain, suggesting it is critical to mitigate exposure to hyperglycaemia and pronounced glucose fluctuations.2-4

Whereas HbA1c goals must be personalized and tailored over time, reaching the HbA1c target of HbA1c below 7% (<53 mmol/mol) remains elusive for most children with T1D. Even fewer attain HbA1c below 6.5% (<48 mmol/mol), a newer consideration, because more stringent goals are associated with better glycaemic outcomes without an increased frequency of acute complications.5,6

Use of continuous glucose monitoring (CGM) is increasing in T1D7 and provides a plethora of data, including time spent in range (TIR; 70-180 mg/dl [3.9-10.0 mmol/L]), below range (TBR; <70 mg/dl [<3.9 mmol/L]), above range (TAR; >180 mg/dl [>10 mmol/L]), and coefficient of variation (CV). These outcome measures, beyond HbA1c, provide data upon which to optimize insulin doses, guide daily decision-making, and inform behavioural modifications.8 Since the inception of CGM, a large body of evidence has accumulated showing its efficacy,9,10 except in very young children with T1D. This study aimed to assess the association of CGM use with real-world glycaemic variability and time in target ranges in a multinational cohort of very young children with T1D on insulin pump therapy. We hypothesized that, like older children and adults, the use of CGM in young children would be associated with diminished glucose excursions and increased TIR.

2 | MATERIALS AND METHODS

The VibRate study (The Effect of Frequent Continuous Glucose Monitoring Use on Glycemic Variability in Preschoolers With T1D) was conducted by ISPAD’s Juniors in Educational Networking and International Research Opportunities: United Sessions (JENIOUS) collaboration. The study protocol was published on the International Society for Pediatric and Adolescent Diabetes (ISPAD) webpage (www.ISPAD.org) in January 2018 and 15 centres from nine countries joined this study (for details, see Appendix S1). Data owners obtained local/national permission for data collection and consented to this analysis and publication. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

The study adopted an open-label, prospective, observational, multinational, registry-based population cohort design to compare glycaemia metrics over 12 months among young children with T1D who were prescribed real-time CGM and those using fingerstick blood glucose monitoring alone (BGM only). Major eligibility criteria included T1D diagnosed at least 6 months prior, age 1-7 years, and insulin pump use for at least 3 months to ensure comparable treatment modality and avoid insulin delivery modality as a confounder.

HbA1c was measured in each centre and standardized to the Diabetes Control and Complications Trial reference of 20-42 mmol/mol (4%-6%).

Additionally, raw CGM/glucometer data files were exported (Appendix S1). Prespecified clinical data were collected during regular clinical visits every 3 months for the 12-month study period and aggregated for each participant. At least 10 days of CGM data at each 3-month time point were required for inclusion in the CGM group analyses and at least 10 days of BGM data with a minimum of five data points per day at each 3-month interval were required for inclusion in the BGM-only group analyses. A reasonable degree of concordance has been shown between outcome measures and frequent intermittent BGM measurements.8,11

The primary endpoint was a difference in glycaemic variability, as measured by the difference in CV between the CGM and BGM-only cohorts, as recommended by the International Consensus on Use of CGM. Other prespecified endpoints were recommended standardized glycaemia metrics (including TIR, TAR, and TBR).12,13 Continuous variables were compared using t tests and χ², or Fisher’s exact tests were used for categorical variables.

The difference between CGM and BGM-only users in glucose metrics8 and proportions of participants achieving recommended goals for time in ranges (TIR > 70%, TBR < 4%, TAR < 25%)14 was assessed with a generalized linear or logistic mixed model, taking glucose monitoring modality (CGM or BGM) as a fixed effect, gender, age, number of glucose measurements, Body Mass Index Standard Deviation Score (BMI SDS), and minority status as covariates, and accounting for centre covariate as a random effect. Pearson’s correlation was used to describe the correlation between the average measured HbA1c value and the calculated (CGM- or BGM-based) TIR or glucose management indicator (GMI) value. According to the Bonferroni correction attributable to multiple comparisons, two-sided P values of less than .005 were considered significant.

A sensitivity analysis was performed to assess glucose outcomes based on BGM data from BGM-only users compared with BGM data from CGM users (at least 10 days of BGM data with a minimum of five
data points per day at 3-month intervals). Statistical analyses were performed with the statistical programming language R version 4.0.2 (2020) (R Foundation for Statistical Computing, Austria) using available packages for descriptive analysis of glucose monitoring data.13

3 | RESULTS

From May 2018 to September 2019, up to 12 months of data from 339 eligible participants were collected from 15 centres. There were 227 participants whose data was sufficient to meet the prespecified analysis requirements (see the study flowchart in Appendix S1). Demographic and clinical characteristics of the study participants are shown in Table 1. The median age at inclusion was 5.3 (1.2-7.9) years. All children used insulin pumps, while 77% (175) were CGM users and 23% (52) were using BGM without CGM (days of data). There were no statistically significant differences in baseline characteristics between the study groups, except for HbA1c ($P = .007$). The characteristics of the ineligible cohort are reported in Appendix S1.

| TABLE 1 Baseline characteristics of study participants |
|-------------------------------------------------------|
| All (n = 227) | CGM (n = 175) | BGM only (n = 52) |
| Age (y) | 5.3 (4.1, 6.4) | 5.2 (4.0, 6.4) | 5.5 (4.7, 6.3) |
| Age at diagnosis (y) | 2.5 (1.6, 3.9) | 2.5 (1.6, 3.8) | 2.6 (1.6, 3.9) |
| Duration of diabetes (y) | 2.1 (1.4, 3.3) | 2.2 (1.5, 3.2) | 2.2 (1.2, 3.4) |
| Body weight (kg) | 20.0 (17.2, 23.0) | 19.6 (17.1, 22.3) | 21.8 (18.2, 23.8) |
| Body height (cm) | 112 (104, 121) | 111 (104, 119) | 115 (108, 121) |
| BMI | 16.1 (15.2, 17.1) | 16.2 (15.2, 17.0) | 16.1 (15.5, 17.1) |
| BMI SDS | 0.7 (0.0, 1.4) | 0.7 (0.0, 1.2) | 0.6 (-0.1, 1.8) |
| Female gender, n (%) | 95 (42) | 78 (45) | 17 (33) |
| Non-Hispanic White (%) | 195 (86) | 147 (84) | 50 (96) |
| HbA1c (%) | 7.2 (6.6, 7.8) | 7.0 (6.5, 7.6)a | 7.6 (7.1, 8.1a) |
| HbA1c (mmol/mol) | 55 (49, 62) | 53 (48, 60)a | 60 (54, 65)a |

Note: Data are median (IQR) or count (%).
Abbreviations: BGM, blood glucose monitoring; BMI, body mass index; BMI SDS, Body Mass Index Standard Deviation Score, calculated based on World Health Organization references; CGM, continuous glucose monitoring.

*There were no statistically significant differences in baseline characteristics between study groups, except for HbA1c ($P = .007$).

FIGURE 1 | A, Time in ranges, and B, Ambulatory glucose profile for children with type 1 diabetes using continuous glucose monitoring (CGM) or blood glucose monitoring (BGM) only. (A) Proportions of time below (<70 mg/dl [3.9 mmol/L]: red), in range (70-180 mg/dl [3.9-10 mmol/L]: green), and above (>180 mg/dl: yellow and orange; >250 mg/dl: orange) glucose range for the CGM and BGM-only cohorts. Estimated differences. (B) Median (solid lines) and interquartile range (IQR; shaded regions) of CGM and BGM-only glucose concentrations over the 24-hour period. Dashed horizontal lines indicate the target glucose range (70 and 180 mg/dl [3.9 and 10 mmol/L]). Non-parametric analyses for data on glucose control (paired non-parametric Wilcoxon signed-rank test) and outcome data are presented as median (IQR), although variables for the analyses utilized mean (glucose concentration, glucose concentration SD). *Estimated differences and $P$ values were derived from a generalized linear mixed model, taking glucose monitoring modality as fixed effect, gender, age at visit, body mass index, number of glucose measurements, and minority status as covariates and centre as random effect. CV, coefficient of variation.
The results of the primary and prespecified secondary efficacy outcomes over the full 24-hour period are presented in Figure 1 and Appendix S1. CGM users had, on average, 93 (IQR 39–145), and BGM users had 95 (61–187) days of data that were used for the analysis. The CV was 39.1% (36.6%–41.9%) among CGM users and 46.8% (42.3%–51.2%) among BGM-only users (estimated mean adjusted difference 8.4% [95% CI: 5.6%–11.2%], P < .001). The proportion of TIR was 65.2% (56.2%–73.0%) in the CGM compared with 49.1% (40.0%–54.5%) in the BGM-only cohort (mean adjusted difference 17.1% [95% CI: 8.8%–25.3%], P < .001), with less pronounced excursions on the ambulatory glucose profile (Figure 1). Median HbA1c over the study period was 7.0% (6.6%–7.6%) in the CGM compared with 7.5% (7.1%–8.1%) in the BGM-only group (estimated adjusted difference 0.8% [95% CI: 0.2%–1.3%], P = .007). The results of the glucose monitoring outcomes for day- and night-time are shown in Appendix S1. In sensitivity analysis, including BGM data from CGM users (118 participants) compared with BGM-only data, CV was lower among CGM users (47.6% vs. 51.3%, mean adjusted difference 3.6% [95% CI: 0.4%–6.9%], P = .031).

The clinical target of TIR more than 70% was achieved by 59 (33.7%) CGM users compared with two (3.8%) BGM-only users (P < .001). Moreover, 104 (59.4%) CGM users achieved the clinical target of TBR less than 4% compared with 16 (30.8%) in the BGM cohort (P < .001). In the CGM group, 47 (26.9%) achieved TAR less than 25% compared with two (3.8%) among BGM-only users (P < .001). Similarly, the recommended HbA1c level of less than 7% (<53 mmol/mol) was achieved by 86 (49.1%) CGM users and by 10 (19.2%) BGM-only users (P < .001).

There was one severe hypoglycaemia event requiring hospitalization in the CGM cohort and four among the BGM-only cohort. Diabetic ketoacidosis occurred twice in one CGM user and did not occur in BGM-only users (Appendix S1).

Among CGM and BGM-only users, HbA1c strongly correlated with TIR (P < .001) and GMI (P < .001) (Appendix S1).

4 DISCUSSION

In this real-world multinational comparison of very young children with T1D treated with insulin pumps, CGM use was associated with reduced glycaemic variability. In the present analysis, youth using CGM were noted to spend approximately 15% more TIR compared with those children not using CGM, when adjusted for other known confounders including age, gender, number of glucose measurements, and minority status. Furthermore, CGM users spent less time above and below range. These results highlight the meaningful clinical impact of CGM in this population, which historically has HbA1c above the recommended targets,9,15 and are encouraging with the median TIR achieved in the CGM group being 65.2% (56.2%–73.0%), approaching the consensus guideline targets of 70% for youth with T1D.

Data from randomized controlled trials (RCTs) on CGM use among very young children with T1D are limited. The first study conducted almost a decade ago used early generation sensor technology in 146 children aged 4 to 10 years.16 While parents were satisfied with CGM, there was no improvement in glycaemia. Less than half of the participants wore this early generation CGM device frequently (six or more days per week), and those with frequent CGM use had greater TIR (51%) than infrequent users (43%). More recently, a large multicentre RCT compared CGM with BGM in a cohort of 143 children with T1D aged 2-8 years over 6 months.17 While there was no significant difference in TIR or HbA1c, the CV improved and TBR was reduced with CGM use, both key findings consistent with the present analysis.

These outcomes are of interest as glycaemic variability has been implicated in damage to the developing brain.2,3 Additionally, the risk of hypoglycaemia is critically dependent on the glucose CV as time in hypoglycaemia less than 70 mg/dL increases almost exponentially with increasing CV, regardless of average glucose level.18 Hence, the relationship of CGM to both diminished glucose variability and reduced hypoglycaemia, even while maintaining HbA1c, could have long-term clinical benefit for very young children with T1D. Consistent with the lower rates of hypoglycaemia in the CGM cohort presented here, there were fewer episodes of severe hypoglycaemia in the RCT described above.17

This is, to our knowledge, the largest prospective multinational real-world analysis of glycaemic metrics beyond HbA1c in very young children with T1D using CGM to date. The strengths of this trial include the heterogeneity of the participant population, because the very young children recruited came from 15 centres in nine countries, and baseline glycaemia varied widely, with HbA1c ranging from 5.5% to 10%.

The challenges inherent to the real-world observational design are the major limitations to this study. Participants in the BGM-only group did not have CGM data collected via a blinded sensor, so the wealth of data generated with CGM may have skewed our results. Nonetheless, Beck and colleagues previously showed a reasonably high degree of concordance between outcomes based on CGM and BGM measurements.12 In our study, relationship analysis showed strong associations between longitudinal HbA1c measurements and both CGM- and BGM-based TIR and GMI, which was previously shown in older individuals with diabetes, in addition to a strong correlation between TBR and CV.19 As CGM is becoming standard of care for young children in many countries,7,20 conducting a clinical trial with BGM use alone while wearing a blinded CGM might face ethical dilemmas.

The current study included only those on pump therapy and therefore extrapolation of our findings to those on multiple daily injections cannot be made. It was not systematically recorded whether suspend at low or predictive low suspend functions were being utilized by those in the CGM group; at the time of the study, however, semi-automated insulin therapy was not yet approved for use in this age range. Further, the study design limited our ability to collect socioeconomic and psychological data, hence we could not control for these possible confounders. As this study included centres from a variety of countries and systems providing healthcare, multiple factors may have impacted participants’ use of CGM and/or pump technology, including availability, access, provider assessment, and family preference.
In summary, our prospective observational analysis of real-world data from very young children with T1D over 12 months complements what has been described in prior controlled research studies; the use of CGM is associated with reduced glucose fluctuations in real-world data, which may better represent very young individuals with T1D compared with those who participate in clinical trials. Despite the heterogeneity of collaborating centres and the unique behavioural challenges in this age group, many young children on pumps who were also using CGM approached targeted glycaemia, as measured by both HbA1c and TIR. Additional long-term studies are needed to determine if CGM, especially when incorporated into semi-automated insulin delivery, will improve outcomes, including daily glycaemia, rates of both acute and chronic complications, and diabetes care-related burden.

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CONFLICT OF INTEREST

KD received honoraria for participation on the speaker’s bureau of Pfizer, Novo Nordisk, and Eli Lilly. JG received speaker’s honoraria from Eli Lilly and Sanofi, and clinical trials investigator’s payment from Novo Nordisk. RM received advisory board honoraria from Abbott and Novo Nordisk. JP received speaker’s honoraria from Medtronic. JS serves as a consultant to Cecelia Health, Lexicon, Lilly, Insulet, Medtronic, and Sanofi, and is a member of the advisory board for Bigfoot Biomedical, Cecelia Health, Insulet, Medtronic, and the T1D Fund and Vertex, and has had research support from the NIH, JDRF, and the Helmsley Charitable Trust. Her institution has had research support from Medtronic and Insulet. AC received speaker’s honoraria from Medtronic, Eli Lilly, and Novo Nordisk. TB received speaker’s honoraria from DexCom, Medtronic, Novo Nordisk, Roche, Sanofi, and Ypsomed, and advisory board honoraria from Ascensia, AstraZeneca, DexCom, Medtronic, and Sanofi.

No other potential conflicts of interest relevant to this study were reported.

AUTHOR CONTRIBUTIONS

KD, MVN, JS, AC, and TB designed the study, participated in data interpretation, and wrote the manuscript. BJB designed the study, performed the statistical analysis, participated in data interpretation, and reviewed and edited the manuscript. ER, CP, GY-M, RM, GF, MM, SHF, JG, JP, and FS researched data and reviewed and edited the manuscript. All authors approved the final version of the manuscript. KD is the guarantor of this work and had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14607.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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