Diabetes Technology & Therapeutics
OnlineFirst

https://doi.org/10.1177/15209156251390819

Sage Journals

Article

Real-World Use of Hybrid Closed-Loop System in Very Young Children with Type 1 Diabetes: Daily Glycemic Patterns Support Glycemic Improvements and Highlight Emerging Challenges for Hypoglycemia

Kevin Perge, MD[1,2,*], Olivier G. Pollé, MD, PhD[3,4,*], Julie Pelicand, MD, PhD[5], Cécile Godot, MD[3], Mélanie Gaudillière, MD[1], Alix Besançon, MD, PhD[3], Gaëlle Vermillac, MD[3], Diletta Ingrosso, MD[3,6], Laura Arvis, MD[1], Michel Polak, MD, PhD[3,7], Marc Nicolino, MD, PhD[1,2], and Jacques Beltrand, MD, PhD[3,7]

Background and Aims: The management of very young children with type 1 diabetes (T1D) presents a considerable challenge for health care teams and the families from glycemic and psychosocial perspectives. The aim of this study was to evaluate the impact of hybrid closed-loop (HCL) system on glycemic control, with a particular focus on the patterns of glycemic parameters throughout the day.

Methods: Seventy-two children under the age of six diagnosed with T1D (diabetes duration ≥6 months) who transitioned to CamAPS-FX-HCL were included. Data were collected prior to (pre-HCL) and at 1, 3, 9, and 12 months following HCL initiation. Pre-HCL and post-HCL periods were compared using linear mixed models.

Results: Time in range ($TIR_{70–180}$) increased by 11% ± 8% from the pre-HCL to 1 month post-HCL ($P < 0.001$), with a concomitant decrease in target above range (TAR_{180}) of 13% ± 9% ($P < 0.001$). The improvement in glycemic control was sustained through 12 months, with the greatest differences observed overnight ($P < 0.001$). Hypoglycemic metrics (TBR_{70}/TBR_{54}) remained similar before and after HCL (all $P > 0.05$). However, hourly glycemic patterns indicated that the late-morning period after HCL initiation was a high-risk period for hypoglycemia with TBR_{70} peaking at 11% ± 9% between 11 AM and 1 PM. This elevated risk of hypoglycemia persisted after 1 year.

Conclusions: In real-life setting, HCL was associated with increased TIR and reduced TAR in very young children with T1D from the first month of use. The present study suggests that late morning is a high-risk window for hypoglycemia in this age group. This finding highlights the importance of optimizing HCL therapy settings and educating parents about specific times of the day that carry a higher risk of glycemic instability.

Keywords

child, glucose variability, hybrid close loop, hypoglycemia, type 1 diabetes, very young children

[1] Pediatric Endocrinology, Diabetology and Metabolism Department, Femme Mère Enfant Hospital, Hospices Civils de Lyon, Bron, France.

[2] Claude Bernard University, Lyon, France.

[3] Department of pediatric endocrinology, gynecology and diabetology, Assistance Publique-Hôpitaux de Paris, Necker Enfants Malades Hospital, Paris, France.

[4] Pediatric Diabetology and endocrinology Unit, CHU Namur, Université Catholique de Louvain, Yvoir, Belgium.

[5] Pediatric Endocrinology, Diabetology and Metabolism Department, Femme Mère Enfant Hospital, CHU of Toulouse, Toulouse, France.

[6] Department of Paediatrics, University of Chieti, Chieti, Italy.

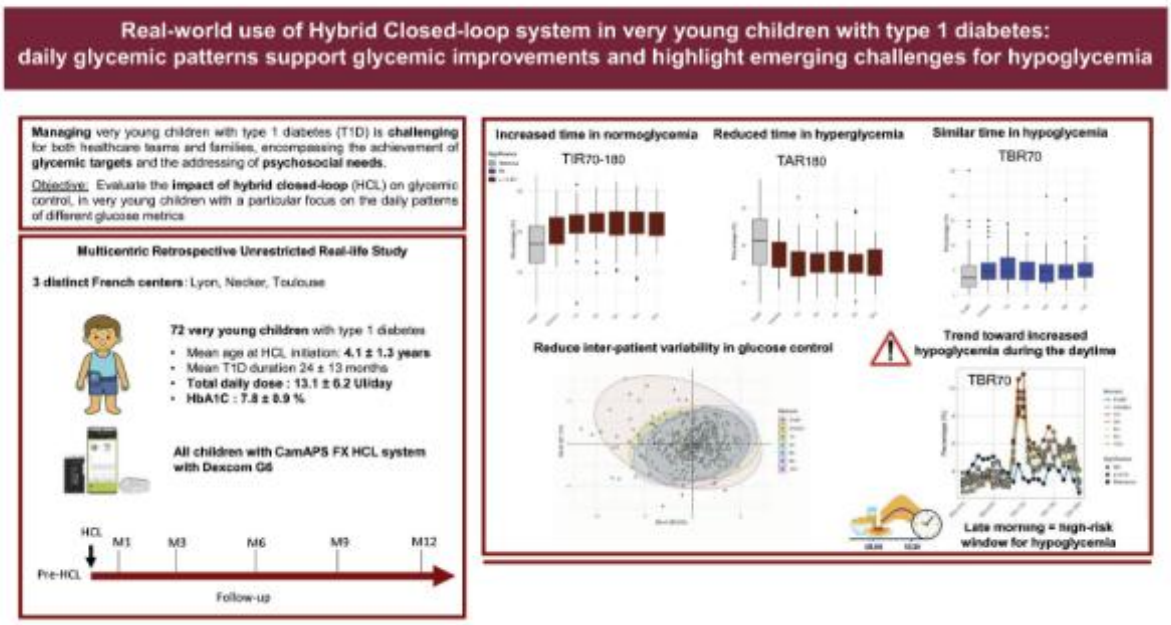
[7] Inserm U 10116, Institut Cochin, Paris, France.

* These authors contributed equally as cofirst authors.

Corresponding author(s):

Kevin Perge, MD, Pediatric Endocrinology, Diabetology and Metabolism Department, Femme Mère Enfant Hospital, Hospices Civils de Lyon, 59 Boulevard Pinel, 69677 Bron, France, kevin.perge@chu-lyon.fr

Real-World Use of Hybrid Closed-Loop System in Very Young Children with Type 1 Diabetes: Daily Glycemic Patterns Support Glycemic Improvements and Highlight Emerging Challenges for Hypoglycemia



Conclusion: Early and stable beneficial effect of the HCL therapy on glycemic control However, challenges persist in this population, due to high glycemic variability and the emergence of specific high-risk windows of hypoglycemia during the day (late morning).

Reference: Kevin Perge, Olivier G. Pollé, Julie Pelicand, Cécile Godot, Mélanie Gaudillière, Alix Besançon, Gaëlle Vermillac, Diletta Ingrosso, Laura Arvis, Michel Polak, Marc Nicolino, and Jacques Beltrand

DOI: 10.1177/15209156251390819

Visual abstract created by Perge et al

Introduction

Recent studies indicate a twofold increase in the incidence of type 1 diabetes (T1D) over the past two decades.[1] Moreover, an even greater increase has been observed in very young children (i.e., below 6 years old).[2] T1D in very young children presents a considerable challenge for health care teams and the children's families from both metabolic and psychosocial perspectives.[3] Achieving glycemic targets in this population is particularly challenging due to their unique characteristics such as highly variable and low insulin needs, as well as unpredictable eating and activity habits.[3–5] Suboptimal metabolic control in very young children is associated with an increased risk of microvascular and macrovascular complications, early cardiovascular disease, and premature death.[6–8] Furthermore, recurrent episodes of hyperglycemia, hypoglycemia, and high glucose variability can detrimentally affect cerebral development, impacting both white and gray matter, and potentially leading to cognitive impairment in adulthood.[9,10] Alterations in both the executive and memory domains were observed within the first year after diagnosis and may be more pronounced when T1D onset occurs at a younger age.[10] Finally, the heavy management burden on parents and caregivers of very young children with T1D has a negative impact on the quality of life of the whole family.[11]

For all these reasons, very young children constitute a particularly important target population for hybrid closed-loop (HCL) systems, which have demonstrated major metabolic improvements in both older children and adults with T1D.[12,13] Several studies in very young children have reported improvements in glycemic outcomes and quality of life.[14–26] Nonetheless, most of these studies did not show improvements in hypoglycemia or glucose variability, nor a reduction in episodes of severe hypoglycemia.[15,18–23,25,26] Notably, the majority of these studies were randomized controlled trials conducted under tightly controlled conditions in relatively small, selected cohorts, which may limit their generalizability to routine clinical practice.[14–23,26] Real-world data corroborate most of the findings of these trials but are scarce.[27] Additional studies, especially in very young children, are therefore essential to support the benefits of HCL systems in broader, unselected populations of people with T1D.[24,25] The objective of this study is to investigate glycemic outcomes and address the unique aspects of HCL use in very young children with T1D. In addition, the study aims to identify glycemic patterns that hinder the achievement of therapeutic goals.

Methods

Study design and participants

This study was designed as a multicenter (Hôpital Universitaire Necker Enfants-Malades, Hospices Civils de Lyon, Hôpital Universitaire of Toulouse) retrospective study to evaluate HCL in very young children with T1D. The study protocol was approved by the ethics committee of Necker Enfants-Malades (number NCK-2024-R-151). In accordance with the prevailing French regulations, parents were informed of the study by post and were granted the option to decline participation. The database was declared to the National Data Protection Commission (Commission Nationale de l'Informatique et des Libertés, CNIL) and registered according to the MR004 protocol.

Children under 6 years of age with T1D for ≥6 months and treated with the CamAPS-FX-HCL system (CamDiab, Cambridge, UK) were included. Few insulin delivery devices are approved for HCL use in this population, and at the time of the study (i.e., 2024), only the CamAPS FX system was reimbursed in France for children between 2 and 6 years.[28] The diagnosis of T1D was made according to the International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines. Exclusion criteria included age ≥6 years at HCL initiation. All participants were switched from open-loop to HCL between November 2023 and November 2024. Initial HCL pump settings and objectives were determined by the physician of the patient according to center-related protocols. Results were therefore adjusted for the center. All functionalities of the pump system (ease-off/boost modes, slow meal absorption, hypoglycemia treatment, snack) were explained to family members at initiation.

At HCL initiation, demographic data (i.e., age, gender), clinical data (i.e., weight and height, age at T1D diagnosis, age at HCL initiation, total daily dose [TDD], glycated hemoglobin [HbA1c]), and raw continuous glucose monitoring (CGM) data were collected to establish pre-HCL values. From the initiation visit, clinical data (weight and HbA1c levels) and pump parameters (i.e., glucose targets, glucose ratios, TDD including the percentage of basal and bolus insulin, percentage of time spent in HCL) were collected at 3, 6, 9, and 12 months.

CGM data

CGM glucose values and insulin basal rates were retrieved from Glooko XT® over the 15 days immediately prior to HCL initiation (pre-HCL) and after the initiation of HCL (i.e., Initiation), and at each subsequent control visit (1, 3, 6, 9, and 12 months). All participants used Dexcom G6®. Glycemic CGM data were analyzed using R software (https://www.R-project.org/, version 4.4.1). CGM data were aggregated using the *cgmanalysis* package and quality-checked using the *Iglu* statistical package.[29] Forty-six CGM metrics were calculated on both a daily and an hourly basis using the *iglu* package.[29] Hourly basal rate was calculated as the mean of basal rates over every 1-h period. The number of boluses per day in the morning time was calculated by summing boluses given between 6:30 AM and 10:00 AM and dividing by the number of days in the CGM period (a value of 1 corresponds to a bolus every day in that interval).

Statistical analysis

All statistical analyses were performed in R. The statistical significance level used for all analyses was 0.05. Demographic and clinical data are reported as the mean ± standard deviation (SD) for continuous variables and as numbers and proportions for categorical variables. Subgroup comparisons were performed according to the glucose control before HCL initiation using the quartiles of HbA1c of the cohort as an exploratory cutoff. We defined two groups corresponding, respectively, to the first two quartiles ("lower quartiles" group; HbA1c below 7.8% [62 mmol/mol; n = 35]) and the upper two quartiles ("higher quartiles" group; HbA1c above 7.8% [62 mmol/mol; n = 37]). Glycemic parameters were adjusted for the center as differences in hypoglycemia were observed between centers. Comparisons between groups were performed using Student's t-test, chi-squared test, or their nonparametric equivalents (Mann–Whitney U test, Fisher exact test, respectively), as appropriate. Pre- vs. post-HCL time points were compared with linear mixed models (lmerTest and lme4 packages), accounting for repeated measures within the same participant.[30] Models included time points (i.e., initiation, 1, 3, 6, 9, and 12 months) and the centers as fixed effects, and patient identity as a random intercept. Post hoc pairwise comparisons of glycemic parameters to pre-HCL were performed using the emmeans package with correction for multiple tests.[31] Principal component analysis (PCA) was conducted in R based on CGM data across all time points (n = 461). Prior to PCA, glucose metrics were standardized and imputed by a regularized expectation—minimization principal component analysis algorithm with the missMDA package.[32]

Results

Participant characteristics

The study included 461 visits from 72 very young children with T1D (mean age at HCL initiation: 4.1 ± 1.3 years; mean T1D duration: 24 ± 13 months). Data included all participants from three French centers meeting the inclusion criteria. Complete data were available for all participants from pre-HCL through 6 months; at 9 and 12 months, data were available for 65 and 45 participants, respectively. Remaining participants had not yet reached the whole follow-up period. No diabetic ketoacidosis or severe hypoglycemia occurred after HCL initiation. Pre-HCL and follow-up characteristics are presented in Table 1.

TABLE 1. CHARACTERISTICS OF PARTICIPANTS BEFORE AND AFTER CLOSED-LOOP INITIATION

	Pre-BF (N = 72)	*Initiation HCL*[a] (N = 71)	*1 month post-HCL* (N = 71)	*3 months post-HCL* (N = 71)	*6 months post-HCL* (N = 71)	*9 months post-HCL* (N = 65)	*12 months post-HCL* (N = 45)
Population characteristics							
Age (years)	4.2 ± 1.3	/	/	/	/	/	/
<4 years, *n* (%)	33 (46)	/					
≥4 years, *n* (%)	39 (54)	/					
Sex—female, *n* (%)	31 (43)	/	/	/	/	/	/
Diabetes duration (years)	2 ± 1.2	/	/	/	/	/	/
Age at diabetes onset (years)	2 ± 1	/	/	/	/	/	/
Age at initiation of HCL (years)	4.2 ± 1.3	/	/	/	/	/	/
Weight (kg)	/	18.2 ± 6.1	/	18.9 ± 3.8	19.9 ± 6.5	19.9 ± 3.5	20.9 ± 3.4
Height (cm)	/	103 ± 11.5	/	105.1 ± 10	107.6 ± 11	108.3 ± 8.6	111 ± 8.9
BMI (kg/m^2)	/	16.7 ± 1.7	/	16.8 ± 1.5	17 ± 1.9	16.8 ± 1.6	16.9 ± 1.7
BMI (Z score)	/	0.7 ± 1.1	/	0.9 ± 1.1	1 ± 1.1	1 ± 1.1	1 ± 1.1
Metabolic control#							
HbA1c (mmol/mol)	62 ± 10	/	/	53 ± 7	52 ± 7	53 ± 9	54 ± 8
HbA1c (%)	7.8 ± 0.9	/	/	7 ± 0.6	6.9 ± 0.6	7 ± 0.7	7.1 ± 0.7
Mean glucose (mg/dL)	175.6 ± 28.7	164.9 ± 16.9	157.2 ± 18.6	156.9 ± 15.5	159.5 ± 16.1	158.7 ± 17.1	156.1 ± 14.7
GMI (%)	7.5 ± 0.7	7.3 ± 0.4	7.1 ± 0.4	7.1 ± 0.4	7.1 ± 0.4	7.1 ± 0.4	7 ± 0.4
Time in range (70–180 mg/dL) (%)	54 ± 13.8	59.9 ± 8.5	63.8 ± 9.1	64.4 ± 8.4	63.5 ± 9.7	63.7 ± 9.3	64.5 ± 8.3
Time in range (70–140 mg/dL) (%)	36.3 ± 12.7	39.2 ± 8.4	43.2 ± 9.1	43.2 ± 8.9	41.7 ± 8.4	42.7 ± 8.5	43.7 ± 7.9
Time above range (>180 mg/dL) (%)	42.3 ± 15.5	35.4 ± 9.2	31 ± 9.7	31 ± 9	31.8 ± 9.7	31.6 ± 9.3	30.6 ± 8.9
Time above range (>250 mg/dL) (%)	17.5 ± 11.5	12.6 ± 6.8	9.9 ± 7	9.3 ± 5.5	10.3 ± 6.4	10.4 ± 7.1	9.3 ± 5.8
Time below range (<70 mg/dL) (%)	4.3 ± 4	5 ± 2.9	5.5 ± 3.4	5 ± 2.7	5 ± 2.8	5.1 ± 2.8	5.2 ± 2.4
Time below range (<54 mg/dL) (%)	1 ± 1.1	1.2 ± 1.2	1.4 ± 1.2	1.2 ± 1	1.4 ± 1.5	1.4 ± 1.4	1.3 ± 1
Coefficient of variation (%)	40.5 ± 6.2	41.9 ± 5.6	40.8 ± 4.8	39.9 ± 4.9	40.4 ± 5.9	40.4 ± 5	40.2 ± 4.7
CONGA	91.7 ± 19.4	89.9 ± 18.3	84.1 ± 16.3	83.4 ± 16.9	85.7 ± 19.3	85.6 ± 17.6	83 ± 15.5
MAGE	105.1 ± 21.3	104.7 ± 18.8	97.2 ± 18.2	94.8 ± 17.1	98.7 ± 20.3	97.6 ± 18.9	95.1 ± 16.2
Pump characteristic							
Total daily dose (IU/d)	13.1 ± 6.2	13.3 ± 4.8	13.9 ± 4.7	14.4 ± 4.8	14.8 ± 4.4	15.2 ± 5.1	15.3 ± 4.7
Total daily dose (IU/d/kg)	0.6 ± 0.3	0.7 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.1
Basal-to-bolus ratio	/	1.1 ± 0.6	1 ± 0.5	1 ± 0.7	1.2 ± 0.8	1.1 ± 0.8	1.2 ± 0.6
Percentage closed-loop	/	87.8 ± 11.8	90.7 ± 13.2	94.7 ± 3.1	94.1 ± 5.7	89.7 ± 13.1	94.3 ± 3.3
Carbohydrate ratios							
Breakfast (g/IU)	/	21.2 ± 11.1	16.1 ± 8	13.9 ± 7.2	14 ± 6.9	13.4 ± 6.5	13.5 ± 5.9
Lunch (g/IU)	/	25.7 ± 11	22.4 ± 9.9	20.6 ± 9.4	21.5 ± 8.4	21.1 ± 8.8	21.9 ± 8.2
Afternoon (g/IU)	/	28.9 ± 16.8	24.3 ± 13.5	22.4 ± 12	24.5 ± 12.8	24.1 ± 13.9	23.8 ± 11.2
Dinner (g/IU)	/	28.2 ± 12.2	25 ± 11.7	22.6 ± 10.9	23.4 ± 9	23.8 ± 10.3	24.8 ± 9.4
Glucose targets						137 ± 18	132 ± 17
Breakfast (mg/dL)	/	141 ± 11	141 ± 15	140 ± 15	138 ± 16	134 ± 14	133 ± 17
Lunch (mg/dL)	/	141 ± 11	138 ± 14	136 ± 13	135 ± 14	131 ± 15	127 ± 15
Afternoon (mg/dL)	/	141 ± 11	138 ± 13	136 ± 14	131 ± 13	122 ± 12	120 ± 11
Evening/night (mg/dL)	/	141 ± 11	129 ± 12	126 ± 13	125 ± 15	122 ± 12	120 ± 11

15 days before HCL, [a] at HCL initiation

Data are the mean ± SD. Percentages may not total 100 because of rounding.
[a]At HCL initiation (calculated on the first 15 days following activation of HCL system).
BMI, body mass index; HCL, hybrid closed-loop; NA, not applicable; SD, standard deviation; GMI, Glucose Management Indicator.

Closed-loop system is associated with increased time in normoglycemia and reduced time in hyperglycemia

After HCL initiation, time in range ($TIR_{70–180}$) and time in tight glucose range ($TITR_{70–140}$) increased within the first month by 11% ± 8% (2.6 h/d) and 8% ± 9% (2 h/d), respectively (Table 1 and Fig. 1B). Both parameters increased across the entire day (all $P < 0.05$) (Fig. 1F). Mean glucose values decreased from 179 ± 28 mg/dL to 157 ± 19 mg/dL after 1 month, and HbA1c levels dropped from 62 ± 10 mmol/mol (7.8% ± 0.9%) to approximately 53 ± 7 mmol/mol (7% ± 0.6%) at 3, 6, 9, and 12 months (all $P < 0.05$). Similarly, GMI declined from 7.5% ± 0.7% to 7.1% ± 0.4% ($P < 0.05$) (Table 1).

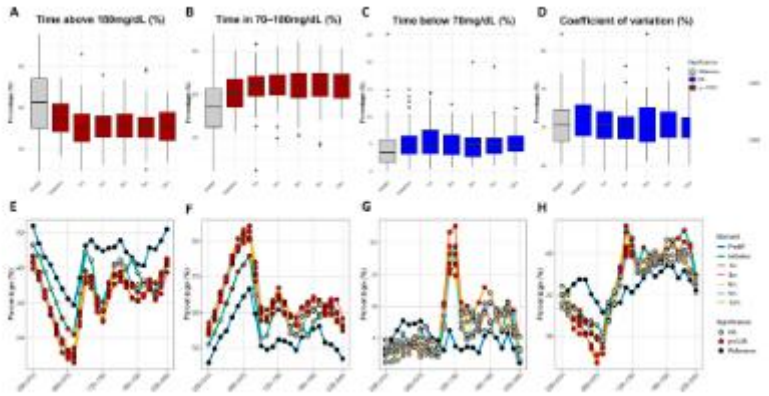


FIG. 1. Evolution of the time spent in different glycemic ranges and coefficients of variation before HCL (reference or dark blue line) and at initiation (green line), 1 month (dark orange line), 3 months (pink line), 6 months (yellow line), 9 months (light blue line), and 12 months (light orange line) postinitiation. Time above 180 mg/dL **(A, E)**, time in range 70–180 mg/dL **(B, F)**, time below 70 mg/dL **(C, G)**, and coefficient of variation **(D, H)** are displayed according to their daily values (A–D) or daily glycemic patterns (E–H). Box plots display the median, 25th, and 75th percentiles. Values were adjusted for the center. Comparisons between pre-HCL and each time point were performed using linear mixed models. The significance level is represented by the color of the boxes or the points (i.e., reference = gray, $P > 0.05$ = blue or dark gray, $P < 0.001$ = dark red). HCL, hybrid closed-loop.

Correspondingly, time above 180 mg/dL (TAR_{180}) decreased by 13% ± 9% within the first month postinitiation (Table 1 and Fig. 1A), and time above 250 mg/dL (TAR_{250}) was halved to <10% (<2.4 h/d) (Table 1). TAR_{180} and TAR_{250} were significantly lower across all hours of the day with HCL, most notably during the nighttime and early morning (Fig. 1E).

After the first month of HCL, parameters of euglycemia and hyperglycemia remained stable (all $P > 0.05$) (Table 1). Accordingly, PCA showed an improvement in these parameters on PC1 (corresponding to euglycemia parameters), with 1 month post-HCL corresponding to the stabilization window of the algorithm (Fig. 2A).

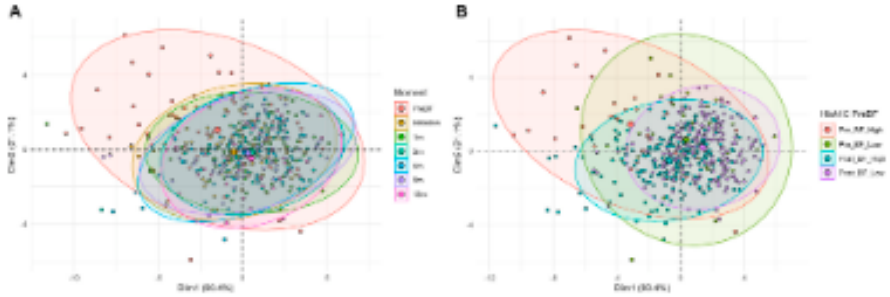


FIG. 2. Representation of glucose homeostasis in young children with type 1 diabetes before (pre-HCL) and at different time points after closed-loop initiation (initiation, 1, 3, 6, 9, and 12 months; $n = 461$). The principal component analysis (PCA) shows the contribution of 46 continuous glucose monitoring (CGM) metrics across two dimensions (PC1 and PC2) **(A** and **B)**. One point corresponds to a patient at a defined time point (*moment*). **(A)** Distribution of glucose homeostasis at different time points, from pre-HCL to 12 months post-HCL. **(B)** Evolution of glucose homeostasis in the subgroup of participants with the highest HbA1c values (i.e., above 7.8%) or the lowest HbA1c (i.e., below 7.8%) before HCL initiation (*pre-BF*) and after HCL initiation. Ellipses define the regions that contain 95% of the group participants (B). The centroids of the ellipses are represented by the dots in bold, colored in the same color as the group and ellipse.

Closed-loop system may reduce variability in glucose homeostasis in children with the highest HbA1c

Initiation of HCL in participants with higher HbA1c in pre-HCL was associated with greater improvements in glycemic metrics, including a larger decrease in TAR_{180} and a larger increase in $TIR_{70–180}$ (Supplementary Table S1). In the first year following HCL initiation, the shift on PC1 was more pronounced in the group with the highest HbA1c in pre-HCL (Fig. 2B). This was associated with a reduction in the interindividual variability of glucose parameters (i.e., SD of parameters) (Table 1), as witnessed by the reduction in the size of the ellipse in PCAs after HCL initiation (Fig. 2A). Nevertheless, participants with higher HbA1c in pre-HCL maintained significantly less optimal glycemic profiles than the group of participants with lower pre-HCL HbA1c at every time point post-HCL (Supplementary Fig. S1). In participants with the highest HbA1c in pre-HCL, a slight but significant increase in time below 54 mg/dL (TBR_{54}) was observed ($P = 0.02$) (Fig. 2B and Supplementary Table S1).

Late morning is a high-risk period for hypoglycemia

Daily time below 70 mg/dL (TBR_{70}), TBR_{54}, and coefficient of variation (CV) remained similar after HCL initiation (all P values >0.05) (Table 1 and Fig. 1C, D). Nonetheless, CV decreased during nighttime (00–06 h AM; $P < 0.01$), contrasting sharply with periods of increased CV and a trend toward increased hypoglycemia during the daytime (Fig. 1E–H). TBR_{70} and TBR_{54} reached their highest values between 11 AM and 1 PM at 1 month (11% ± 9% and 3% ± 4%, respectively). This peak followed, on the one hand, a steep rise in mean glucose and TAR_{180} (Fig. 1E and Supplementary Fig. S2) and, on the other hand, a marked increase in basal insulin (i.e., up to 250%) between 8 AM and 10 AM, preceded by a period of relative insulinopenia in the early morning (i.e., 4 AM to 7 AM) (Fig. 3A). While the percentage of hypoglycemia slightly decreased from 3 months post-HCL, the pattern of basal insulin rise in the 2 h preceding episodes of late-morning hypoglycemia persisted across later follow-ups (Fig. 3), despite adjustment for centers. Carb ratios were often slightly higher (i.e., less aggressive) than theoretical values (i.e., 300 rule) at HCL initiation (i.e., respectively 26 ± 11 g/IU vs. 24 ± 7 g/IU) (Table 1).[33] These ratios were progressively decreased over the subsequent months, particularly in the morning (Table 1). This gradual adaptation of ratios was accompanied by a slight reduction in early-morning basal insulin peaks in the months following HCL initiation (Fig. 3A). Nonetheless, late-morning hypoglycemia persisted at 12 months post-HCL (Fig. 1G, H). Subanalysis including only visits with more than 0.9 bolus per day in the morning time showed a similar pattern of hypoglycemia (n = 287, 62%) (Supplementary Fig. S3).

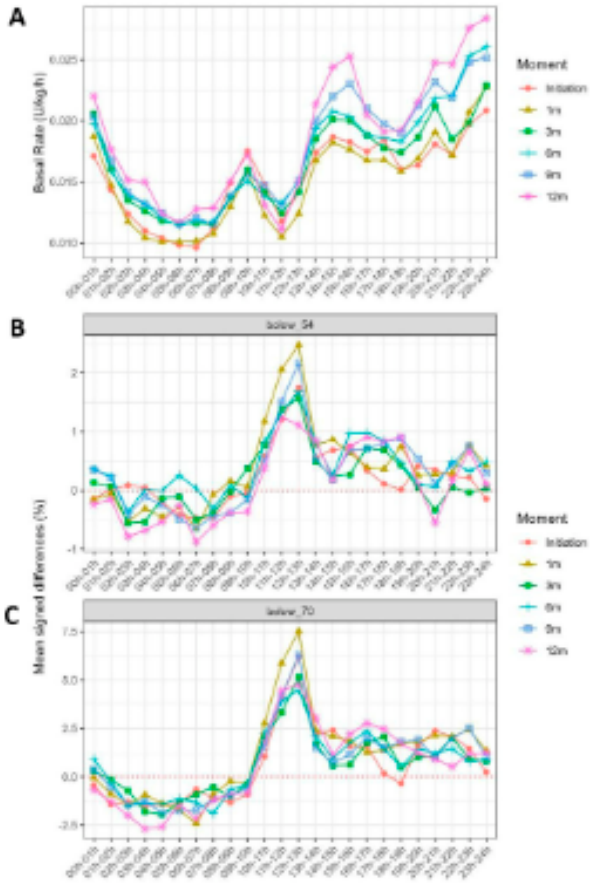


FIG. 3. Evolution of insulin basal rate and hypoglycemia across the day after HCL initiation. **(A)** Evolution of insulin basal rate normalized for weight during the nycthemere. Evolution of absolute difference in time spent below 54 mg/dL **(B)** and time spent below 70 mg/dL **(C)** between pre-HCL and each post-HCL time point. Differences were calculated by subtracting pre-HCL values from post-HCL values at each time point. The dashed red line corresponds to the pre-HCL baseline.

Upon initiation of HCL, the majority of participants were using a single (94%) and relatively high glucose target during the entire day (mean glucose target: 141 mg/dL). The adoption of multiple, lower glucose targets emerged from 1 month post-HCL and progressed over time with notably lower targets during the nighttime (Table 1 and Supplementary Fig. S4). Participants with lower nighttime glucose targets exhibited higher $TIR_{70–180}$ and $TITR_{70–140}$ and fewer hypoglycemic episodes (data not shown).

Discussion

Our study suggests that HCL systems improve overall glucose homeostasis in very young children by increasing the $TIR_{70–180}$ and decreasing the TAR_{180} without a concomitant rise in hypoglycemia. However, an in-depth analysis of daily CGM profiles identified the late-morning period as a high-risk window for hypoglycemia, accompanied by increased glycemic variability.

These findings are in line with earlier studies showing improved glycemic control from the first months of HCL in the pediatric population, with benefits maintained over at least 12 months.[14–26] We observed that the largest gains in TIR occurred overnight, reflecting the efficiency of the system during fasting periods but also its relative limitations during times of carbohydrate intake. Significantly, the use of HCL appeared to reduce the disparity in glycemic control between children with elevated HbA1c levels and those with lower HbA1c levels. Those with the highest HbA1c levels at pre-HCL exhibited the most substantial enhancements in glucose homeostasis. However, this subgroup demonstrated only a marginal increase in hypoglycemia. Even so, and consistent with previous studies, only 13% of participants reached current ISPAD glycemic targets ($TIR_{70–180}$ >70% and TBR70 <4%) after 6 months of HCL use, underscoring the persistent challenges in reaching optimal glucose control in very young children compared with older cohorts.[13,26,34–35]

Glucose variability is characterized by both its amplitude and temporal patterns, two features that are of particular importance for the patient's well-being and brain development in this age group.[9,10] HCL use was associated with a decrease in both the amplitude (i.e., MAGE) and the reproducibility (i.e., MODD and CONGA) of glucose variability,[36] even though the overall CV did not change appreciably (Table 1 and Supplementary Fig. S5). We observed a pronounced dichotomy between nighttime and daily variability with overnight glucose fluctuations being markedly reduced with HCL, whereas daytime variability remained high likely owing to rapid postprandial spikes. This day–night pattern corresponds to the late-morning peak in hypoglycemia, since greater intraday variability often accompanies hypoglycemia.[37]

Hypoglycemia in very young children with T1D remains more frequent than in other children.[21,38] Consistent with previous studies,[15,18–23,25,26] initiation of HCL did not significantly reduce overall hypoglycemic exposure in our cohort. We therefore examined the daily distribution of hypoglycemic episodes and identified distinct peaks during postprandial periods with the highest values observed in the late morning. Similar observations were recently described by another team.[38] While the use of highly conservative carbohydrate ratios at HCL initiation may partially explain this pattern in our cohort, late-morning hypoglycemia persisted at 12 months even when breakfast boluses were given, ratios optimized, and results adjusted for center. Additional factors may contribute to this phenomenon: very young children exhibit important fluctuations in insulin requirements due to high insulin sensitivity in the morning (with a period of relative insulinopenia before breakfast), followed by a period of insulin-resistance during nocturnal secretion of growth hormone.[39] Additionally, very young children exhibit unpredictable eating and physical activity habits that may lead to substantial changes in insulin requirements.[3] These factors may result in insufficient insulin delivery in the morning time, with postprandial hyperglycemia and late-morning hypoglycemia ensuing.[3–5,38,40] The role of relative insulinopenia at the end of the night may have been previously underestimated and may contribute to this phenomenon, especially if the bolus timing is suboptimal[41] and the meal is composed of rapidly absorbed carbohydrates (as observed in France).

Current HCL algorithms remain challenged by rapid glucose excursions in this age group, as even fast-acting insulin analogues cannot counter the rapid glycemic fluctuations.[42] Our findings emphasize the importance of careful meal management, including the administration of boluses 10–15 min before food intake to mitigate large postprandial spikes. Nonetheless, caution is warranted if the child may not be eating at the expected time or will not eat as much as expected: the initial announcement of at least 50% of expected carbohydrates should be made 10–15 min before the meal, followed by a second announcement at the end with the remaining carbohydrates. Regular evaluation of insulin-to-carb ratios is also crucial with ratios often ending up below the theoretical value.[33] When possible, another potential approach may be to lower glycemic targets 2 h before breakfast (early morning) to encourage insulin delivery before the meal, though this strategy requires further investigation. If late-morning hypoglycemia persists, additional interventions may include setting temporarily higher glucose targets (e.g., ease-off mode) or providing a mid-morning snack. However, this may lead to a substantial increase in burden for parents, which has already been shown to be high in parents of young children with T1D.[11] It is therefore important to educate parents of very young children with T1D about the risk of late-morning hypoglycemia in the first month following HCL initiation and to work with families to identify potential preventive measures (Table 1 and Fig. 1G).

Our data also support the use of different glucose targets over the course of the day to optimize glycemic outcomes, with the highest values during the daytime and the lowest during nighttime. A recent study found that lower targets can result in an increase in TBR_{70}.[43] In our cohort, lower glucose targets during nocturnal periods were associated with improved glycemic outcomes and a reduction in hypoglycemic episodes. A lower glucose target likely prompts earlier and gentler insulin delivery, limiting hyperglycemic excursions with more reliable and appropriately dosed insulin deliveries. Prospective studies are needed to confirm the safety and efficacy of such target adjustments.

The present study has several strengths, including the description of an unrestricted real-life study design, which enhances the external validity and clinical relevance.[44] Furthermore, the present study included a large number of children from three geographically distinct French expert centers, with an average age at HCL initiation that was lower than in previous studies.[14–26] To our knowledge, it is the first study to combine an hourly analysis of glycemic patterns with insulin delivery data in this age group, providing unique insights for clinical practice. Additionally, we evaluated very early postinitiation outcomes (from 2 weeks post-HCL initiation), which enabled us to detect short-term challenges such as periods of high risk of hypoglycemia.

The present study was limited by its retrospective design and the lack of a parallel control group using standard therapy. Nonetheless, the primary objective was to depict the evolution of glucose homeostasis after HCL, rather than to compare it with an open-loop system. Center-specific differences in pump settings and adaptation practices (e.g., adjustments of ratios or targets) may have influenced outcomes; we partially accounted for this by including the center as a covariate in our models. We also did not assess psychosocial outcomes, such as quality of life or sleep, which are important considerations in pediatric diabetes management. In addition, we stratified participants using an exploratory HbA1c cutoff of 7.8%, which corresponded to the median HbA1c in our cohort. This cutoff is knowingly higher than the <6.5% target recommended by current guidelines for toddlers but was chosen to reflect our cohort's glycemic distribution. Finally, our observations regarding specific glycemic patterns (e.g., late-morning hypoglycemia) pertain to the particular HCL system used (CamAPS FX) and our study population and may not be fully generalizable to other automated insulin delivery systems or patient groups.

In conclusion, our study showed an early and stable beneficial effect of the HCL therapy on glycemic control, characterized by a reduction in hyperglycemia, an increase in euglycemia, and no overall increase in hypoglycemia. However, challenges persist in this population due to high glycemic variability and the emergence of specific high-risk periods for hypoglycemia during the day. Close collaboration between the diabetes team and the family is essential to optimize HCL therapy and reach recommended glycemic targets in very young children with T1D.

Authors' Contributions

K.P., O.G.P., and J.P. researched data, performed formal analysis, contributed to discussion, and wrote the first draft of the article. C.G., M.G., A.B., G.V., D.I., L.A., and M.P. researched data and reviewed and edited the article. M.N. and J.B. contributed to discussion and reviewed and edited the article. All authors approved the final version of the article.

References

1. Ogle GD, Wang F, Haynes A, et al. Global type 1 diabetes prevalence, incidence, and mortality estimates 2025: Results from the International diabetes Federation Atlas, 11th Edition, and the T1D Index Version 3.0. *Diabetes Res Clin Pract*, 2025; 225:112277; Crossref
2. Patterson CC, Harjutsalo V, Rosenbauer J, et al. Trends and cyclical variation in the incidence of childhood type 1 diabetes in 26 European centres in the 25 year period 1989–2013: A multicentre prospective registration study. *Diabetologia*, 2019; 62(3):408–417; Crossref
3. Sundberg F, deBeaufort C, Krogvold L, et al. ISPAD clinical practice consensus guidelines 2022: Managing diabetes in preschoolers. *Pediatr Diabetes*, 2022; 23(8):1496–1511; Crossref
4. Dovc K, Boughton C, Tauschmann M, et al.; APCam11, AP@Home, and KidsAP Consortia. Young children have higher variability of insulin requirements: Observations during hybrid closed-loop insulin delivery. *Diabetes Care*, 2019; 42(7):1344–1347; Crossref
5. Sandy JL, Tittel SR, Rompicherla S, et al.; Prospective Diabetes Follow-Up Registry Initiative (DPV). Demographic, clinical, management, and outcome characteristics of 8,004 young children with type 1 diabetes. *Diabetes Care*, 2024; 47(4):660–667; Crossref
6. Nathan DM, for the DCCT/EDIC Research Group. The diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: Overview. *Diabetes Care*, 2014; 37(1):9–16; Crossref
7. Magliano DJ, Harding JL, Shaw JE. Glycemic control and excess mortality in type 1 diabetes. *N Engl J Med*, 2015; 372(9):880; Crossref
8. 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(10146):477–486; Crossref
9. Gaudieri PA, Chen R, Greer TF, et al. Cognitive function in children with type 1 diabetes. *Diabetes Care*, 2008; 31(9):1892–1897; Crossref
10. Mauras N, Buckingham B, White NH, et al.; Diabetes Research in Children Network (DirecNet). Impact of type 1 diabetes in the developing brain in children: A longitudinal study. *Diabetes Care*, 2021; 44(4):983–992; Crossref
11. Kimbell B, Lawton J, Boughton C, et al. Parents' experiences of caring for a young child with type 1 diabetes: A systematic review and synthesis of qualitative evidence. *BMC Pediatr*, 2021; 21(1):160; Crossref
12. Di Molfetta S, Di Gioia L, Caruso I, et al. Efficacy and safety of different hybrid closed loop systems for automated insulin delivery in people with type 1 diabetes: A systematic review and network meta-analysis. *Diabetes Metab Res Rev*, 2024; 40(6):e3842; Crossref
13. Zeng B, Gao L, Yang Q, et al. Automated insulin delivery systems in children and adolescents with type 1 diabetes: A systematic review and meta-analysis of outpatient randomized controlled trials. *Diabetes Care*, 2023; 46(12):2300–2307; Crossref
14. Sherr JL, Bode BW, Forlenza GP, et al.; Omnipod 5 in Preschoolers Study Group. Safety and glycemic outcomes with a tubeless automated insulin delivery system in very young children with type 1 diabetes: A single-arm multicenter clinical trial. *Diabetes Care*, 2022; 45(8):1907–1910; Crossref
15. Wadwa RP, Reed ZW, Buckingham BA, et al.; PEDAP Trial Study Group. Trial of hybrid closed-loop control in young children with type 1 diabetes. *N Engl J Med*, 2023; 388(11):991–1001; Crossref

16. Ware J, Allen JM, Boughton CK, et al.; KidsAP Consortium. Randomized trial of closed-loop control in very young children with type 1 diabetes. *N Engl J Med*, 2022; 386(3):209–219; Crossref

17. Kimbell B, Rankin D, Hart RI, et al.; KidsAP consortium. Parents' experiences of using a hybrid closed-loop system (CamAPS FX) to care for a very young child with type 1 diabetes: Qualitative study. *Diabetes Res Clin Pract*, 2022; 187:109877; Crossref

18. Pulkkinen MA, Varimo TJ, Hakonen ET, et al. MiniMed 780G™ in 2- to 6-year-old children: Safety and clinical outcomes after the first 12 weeks. *Diabetes Technol Ther*, 2023; 25(2):100–107; Crossref

19. Rapini N, Martino M, Arnaldi C, et al. Efficacy and safety of advanced hybrid closed loop systems in children with type 1 diabetes younger than 6 years. *Front Endocrinol*, 2024; 15; Crossref

20. Pulkkinen M-A, Varimo TJ, Hakonen ET, et al. During an 18-month course of automated insulin delivery treatment, children aged 2 to 6 years achieve and maintain a higher time in tight range. *Diabetes Obes Metab*, 2024; 26(6):2431–2438; Crossref

21. Ware J, Allen JM, Boughton CK, et al.; KidsAP Consortium. Eighteen-Month hybrid closed-loop use in very young children with type 1 diabetes: A single-arm multicenter trial. *Diabetes Care*, 2024; 47(12):2189–2195; Crossref

22. Seget S, Chobot A, Rusak E, et al. MiniMed 780GTM in children with type 1 diabetes under seven years of age: Prospective open-label, single-arm, double-center, follow-up study. *Technol Health Care*, 2024; 32(3):1463–1472; Crossref

23. DeSalvo DJ, Bode BW, Forlenza GP, et al. Glycemic outcomes persist for up to 2 years in very young children with the Omnipod® 5 automated insulin delivery system. *Diabetes Technol Ther*, 2024; 26(6):383–393; Crossref

24. Tornese G, Carletti C, Lanzetta MA, et al. Safety of real-life usage of advanced hybrid closed-loop system MiniMed 780G in children with type 1 diabetes younger than 7 years old. *Diabetes Care*, 2023; 46(6):e123–e125; Crossref

25. Alwan H, Wilinska ME, Ruan Y, et al. Real-World evidence analysis of a hybrid closed-loop system. *J Diabetes Sci Technol*, 2025; 19(2):385–389; Crossref

26. Battelino T, Kuusela S, Shetty A, et al.; LENNY study group. Efficacy and safety of automated insulin delivery in children aged 2–6 years (LENNY): An open-label, multicentre, randomised, crossover trial. *Lancet Diabetes Endocrinol*, 2025; 13(8):662–673; Crossref

27. Biester T, Berget C, Boughton C, et al. International society for pediatric and adolescent diabetes clinical practice consensus guidelines 2024: Diabetes technologies—insulin delivery. *Horm Res Paediatr*, 2024; 97(6):636–662; Crossref

28. Arrêté Du 3 Octobre 2023 Portant Inscription Du Système de Boucle Semi-Fermée Dédié à La Gestion Automatisée Du Diabète de Type I MYLIFE CAMAPS FX de La Société YPSOMED Au Titre I de La Liste Des Produits et Prestations Remboursables Prévue à l'article L. 165-1 Du Code de La Sécurité Sociale - Légifrance. n.d. Available from: https://www.legifrance.gouv.fr/jorf/id/JORFTEXT000048158973 [Last accessed: February3, 2025].

29. Chun E, Fernandes NJ, Gaynanova I. An update on the iglu software package for interpreting continuous glucose monitoring data. *Diabetes Technol Ther*, 2024; 26(12):939–950; Crossref

30. Bates D, Mächler M, Bolker B, et al. Fitting linear mixed-effects models using lme4. *J Stat Soft*, 2015; 67(1):1–48; Crossref

31. Lenth R, Lenth MR. (2018) Package 'lsmeans'. *Am Stat*, 2018; 34(4):216–221.

32. Josse J, Husson F. missMDA: A package for handling missing values in multivariate data analysis. *J Stat Soft*, 2016; 70(1)–:31; Crossref

33. Cengiz E, Danne T, Ahmad T, et al. ISPAD clinical practice consensus guidelines 2022: Insulin treatment in children and adolescents with diabetes. *Pediatr Diabetes*, 2022; 23(8):1277–1296; Crossref

34. Henry Z, Fimbel SV, Bendelac N, et al. Beneficial effects of automated insulin delivery over one-year follow-up in real life for youths and adults with type 1 diabetes irrespective of patient characteristics. *Diabetes Obes Metab*, 2024; 26(2):557–566; Crossref

35. 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(8):1593–1603; Crossref

36. Guilmin-Crépon S, Carel JC, Schroedt J, et al. How should we assess glycemic variability in type 1 diabetes? contribution of principal component analysis for interstitial glucose indices in 142 children. *Diabetes Technol Ther*, 2018; 20(6):440–447; Crossref

37. Monnier L, Colette C, Wojtusciszyn A, et al. Toward defining the threshold between low and high glucose variability in diabetes. *Diabetes Care*, 2017; 40(7):832–838; Crossref

38. Alwan H, Ware J, Boughton CK, et al. Time spent in hypoglycemia according to age and time of day: Observations during closed-loop insulin delivery. *Diabetes Technol Ther*, 2023; 25(7):485–491; Crossref

39. Holterhus PM, Odendahl R, Oesingmann S, et al.; German Pediatric CSII Working Group. Classification of distinct baseline insulin infusion patterns in children and adolescents with type 1 diabetes on continuous subcutaneous insulin infusion therapy. *Diabetes Care*, 2007; 30(3):568–573; Crossref

40. Fuchs J, Hovorka R. Benefits and challenges of current closed-loop technologies in children and young people with type 1 diabetes. *Front Pediatr*, 2021; 9:679484; Crossref

41. Coutant R, Bismuth E, Bonnemaison E, et al. Hybrid closed loop overcomes the impact of missed or suboptimal meal boluses on glucose control in children with type 1 diabetes compared to sensor-augmented pump therapy. *Diabetes Technol Ther*, 2023; 25(6):395–403; Crossref

42. Ware J, Allen JM, Boughton CK, et al. Hybrid closed-loop with faster insulin aspart compared with standard insulin aspart in very young children with type 1 diabetes: A double-blind, multicenter, randomized, crossover study. *Diabetes Technol Ther*, 2023; 25(6):431–436; Crossref

43. Fattah M, Boughton CK, Ware J, et al. Evaluating the impact of applying personal glucose targets in a closed-loop system for people with type 1 diabetes. *J Diabetes Sci Technol*, 2024; 18(3):695–700; Crossref

44. Dang A. Real-World evidence: a primer. *Pharmaceut Med*, 2023; 37(1):25–36; Crossref