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ORIGINAL ARTICLE

Predictors of Time-in-Range (70–180 mg/dL) Achieved Using a Closed-Loop Control System

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Abstract

Background: Studies of closed-loop control (CLC) in patients with type 1 diabetes (T1D) consistently demonstrate improvements in glycemic control as measured by increased time-in-range (TIR) 70–180 mg/dL. However, clinical predictors of TIR in users of CLC systems are needed.

Materials and Methods: We analyzed data from 100 children aged 6–13 years with T1D using the Tandem Control-IQ CLC system during a randomized trial or subsequent extension phase. Continuous glucose monitor data were collected at baseline and during 12–16 weeks of CLC use. Participants were stratified into quartiles of TIR on CLC to compare clinical characteristics.

Results: TIR for those in the first, second, third, and fourth quartiles was 54%, 65%, 71%, and 78%, respectively. Lower baseline TIR was associated with lower TIR on CLC ($r = 0.69$, $P < 0.001$). However, lower baseline TIR was also associated with greater improvement in TIR on CLC ($r = -0.81$, $P < 0.001$). During CLC, participants in the highest versus lowest TIR-quartile administered more user-initiated boluses daily (8.5 ± 2.8 vs. 5.8 ± 2.6, $P < 0.001$) and received fewer automated boluses (3.5 ± 1.0 vs. 6.0 ± 1.6, $P < 0.001$). Participants in the lowest (vs. the highest) TIR-quartile received more insulin per body weight (1.13 ± 0.27 vs. 0.87 ± 0.20 U/kg/d, $P = 0.008$). However, in a multivariate model adjusting for baseline TIR, user-initiated boluses and insulin-per-body-weight were no longer significant.

Conclusions: Higher baseline TIR is the strongest predictor of TIR on CLC in children with T1D. However, lower baseline TIR is associated with the greatest improvement in TIR. As with open-loop systems, user engagement is important for optimal glycemic control.

Keywords: Closed-loop systems, Type 1 diabetes, Insulin pump, Time-in-range.

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Introduction

Management of type 1 diabetes (T1D) in childhood is challenging, and only a small percentage of children achieve the recommended glycemic targets.[1] Before the advent of newer diabetes technologies, the primary modifiable predictor of glycemic control as measured by HbA1c was the frequency of blood glucose monitoring.[2]

Over the past several years, use of continuous glucose monitoring (CGM) has increased rapidly in children with T1D.[1] As expected, CGM use in children is associated with improved glycemic outcomes regardless of the modality of insulin delivery used.[1,3] With increased use of CGM technology, metrics of glycemic control have shifted to CGM-based outcomes, primarily time-in-range (TIR), defined by a target of 70–180 mg/dL. Recently established CGM-based glycemic targets recommend TIR >70% with additional out-of-range targets of <5% above 250 mg/dL, <25% above 180 mg/dL, <4% under 70 mg/dL, and <1% under 54 mg/dL.[4]

Closed-loop control (CLC) systems (also referred to as artificial pancreas or automated insulin delivery systems), which utilize CGM data along with a predictive algorithm to automatically adjust basal insulin delivery and in some instances give automated correction boluses, have consistently been shown to increase TIR in children and adults with T1D.[5–8] Published trials of Food and Drug Administration (FDA)-approved hybrid CLC systems have reported achieving a mean TIR just above the goal of >70% in users.[5,8] However, not all users benefit from CLC equally and are able to meet this metric. The clinical characteristics of users who are able to achieve the highest (and lowest) TIR on CLC are of significant interest to clinicians hoping to optimize this new treatment modality for individuals with T1D.

We conducted a 16-week randomized clinical trial (RCT) comparing the Tandem t:slim X2 Control-IQ hybrid Control-IQ CLC system versus a sensor-augmented pump (SAP) in 6–13-year-olds and found this CLC system to be safe and effective.[9] Following the RCT, the SAP group used the CLC system for 12 weeks.[10] We utilized the data from this study to determine predictors of TIR while using this CLC system. We hypothesized that children with higher TIR using CLC would have better glycemic control at baseline, spend more time in CLC, and demonstrate higher levels of user engagement with a greater number of carbohydrate boluses per day.

Materials and Methods

The Diabetes Closed Loop—Protocol 5 (DCLP5) RCT was conducted at four pediatric diabetes centers in the United States (clinicaltrials.gov registration NCT03844789). The protocol was approved by a central Institutional Review Board (Tampa, FL), written informed consent was obtained from the parent or guardian of each participant, and assent was obtained from each participant when applicable. An Investigational Device Exemption was approved by the U.S. Food and Drug Administration. The protocol has previously been reported in detail[9] and is available at NEJM.org. Major inclusion criteria were age 6–<14 years, T1D diagnosed for at least 1 year, use of insulin for at least 6 months, and a total daily insulin dose of at least 10 U.

In brief, between June 6, 2019 and March 20, 2020, 101 children 6–13 years old were randomized in a 3:1 ratio to use CLC on a Tandem t:slim X2 insulin pump with Control-IQ Technology and a DexCom G6 CGM ($n = 78$) or SAP ($n = 22$) for 16 weeks. This randomization phase was followed by a 12-week extension phase, during which the SAP group transitioned to CLC and the CLC group continued on the system.[10] Participants' pump, CGM, glucose meter, and ketone meter data were downloaded and reviewed multiple times throughout the course of the study. HbA1c was measured at a central laboratory at enrollment, the end of the randomization phase, and the end of the extension phase.

Statistical analysis

For the purposes of this study ''baseline'' refers to the time period before initiating CLC, which was during the pre-randomization phase for those randomized to CLC at study onset and during the randomization phase for those who were in the SAP group who subsequently transitioned to CLC. For the group randomized to CLC at study onset, baseline CGM metrics were calculated from either the 2 weeks before

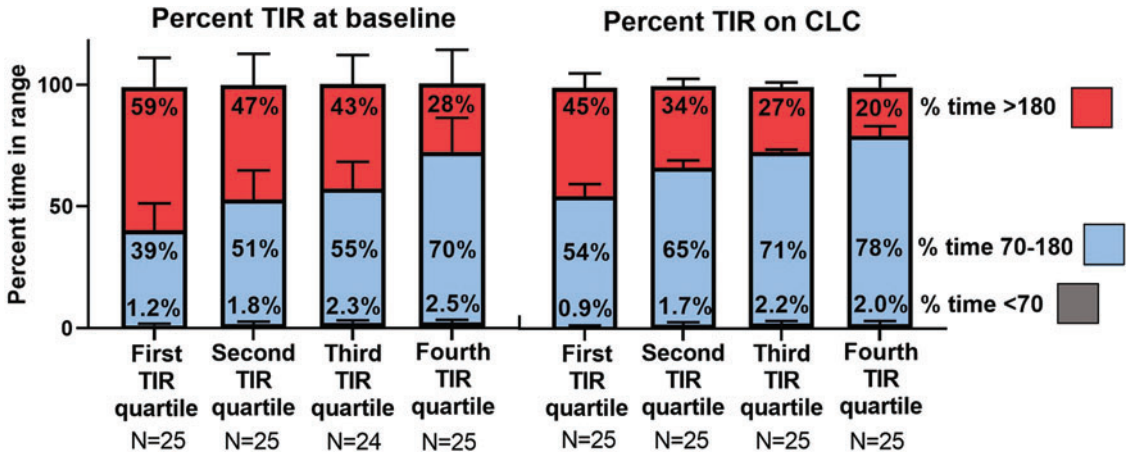

FIG. 1. Mean TIR at baseline and on CLC by quartile of TIR on CLC. Red represents percent time >180 mg/dL. Blue represents percent time 70–180 mg/dL. Gray represents percent time <70 mg/dL. CLC, closed-loop control; TIR, time-in-target range. Color images are available online.

enrollment or from a 2-week run-in phase (required for CGM or insulin pump naive participants), and CLC data were from the 16-week randomization phase. For the group randomized to SAP, baseline CGM metrics were calculated from the randomized trial phase and the CLC TIR data from the 12-week extension phase.[10] Both randomization groups showed a similar increase in TIR on CLC compared with baseline,[9] thus, the CLC TIR data for both of these groups were combined for the current analysis.

Participants were categorized into four groups based on quartiles of TIR while using CLC. These groups were created for the purpose of tabulating the data only. All models were based on TIR as a continuous variable.

To assess the association of demographic, clinical, and system use characteristics with TIR while using CLC, univariate linear regression models were fit with continuous TIR at follow-up as the dependent variable and the characteristic as the predictor. In addition, a multivariate linear regression model was fit with continuous TIR at follow-up as the dependent variable and all characteristics included as predictors. To avoid multicollinearity, some characteristics were not included in the multivariate model. *P*-values are two-sided and have been adjusted for multiple comparisons to control the false discovery rate using the adaptive Benjamini-Hochberg procedure.[11] Analyses were conducted with SAS software version 9.4 (SAS Institute, Inc., Cary, NC).

Results

Of the 101 children in the clinical trial, one participant in the SAP group dropped out during the randomization phase and 100 completed the study. Seventy-eight participants first used the CLC system during the randomization phase and the remaining 22 in the SAP group went on to use the CLC system during the extension phase.[10] Age range at the time of initiation of CLC was 6.5–14.3 years (mean ± SD 11.2 ± 2.0), duration of T1D was 1.2–13.0 years (mean 5.3 ± 2.9), and baseline HbA1c was 5.6%–10.0% (mean 7.6% ± 1.0%). Baseline characteristics of the entire cohort by intervention group have been previously published.[9]

The cohort was divided into quartiles based on TIR while on CLC using the following cut points: 59%, 69%, and 73%. TIR according to quartile is shown in Figure 1. Mean TIR on CLC for those in the first, second, third, and fourth quartiles was 54%, 65%, 71%, and 78%, respectively. Time above 180 mg/dL was higher for the lowest TIR quartile compared with the highest quartile (mean 45% vs. 20%) (Table 1). Time below 70 mg/dL was low for all groups but was higher in the highest TIR quartile compared with the lowest (median 1.66% vs. 0.80%).

There was a strong correlation between TIR at baseline and TIR on CLC ($r = 0.69$, $P < 0.001$, Fig. 2A). However, those with lower TIR at baseline had greater improvement in TIR after the initiation of CLC ($r = -0.81$, $P < 0.001$, Fig. 2B). Those with lower HbA1c at baseline tended toward more TIR on CLC (Fig. 2C).

The TIR on CLC quartile groups did not differ with respect to age, duration of diabetes, BMI percentile, weight, or family income at baseline (Table 2). Fewer participants were CGM users before enrollment in the lowest quartile compared to the highest quartile (88% vs. 100%; $P = 0.02$).

TABLE 1. GLYCEMIC OUTCOMES BY TIME-IN-RANGE DURING CLOSED-LOOP CONTROL

	Time-in-range 70–180 mg/dL during CLC[a]				
	First quartile (n = 25)	*Second quartile* (n = 25)	*Third quartile* (n = 25)	*Forth quartile* (n = 25)	*Univariate*, P[b]
Baseline glycemic measures					
Time-in-range 70–180 mg/dL	39% ± 11%	51% ± 12%	55% ± 11%	70% ± 14%	<0.001
Mean glucose (mg/dL)	212 ± 27	187 ± 25	178 ± 21	152 ± 23	<0.001
Time >180 mg/dL	59% ± 12%	47% ± 13%	43% ± 12%	28% ± 14%	<0.001
Time <70 mg/dL	0.73% (0.08%, 1.40%)	1.78% (0.57%, 2.56%)	1.46% (0.75%, 3.17%)	1.90% (0.98%, 2.86%)	0.008
HbA1c (%)	8.6 ± 0.7	7.6 ± 0.6	7.5 ± 0.7	6.8 ± 0.7	<0.001
Glycemic measures during CLC					
Time-in-range 70–180 mg/dL	54% ± 5%	65% ± 3%	71% ± 1%	78% ± 4%	NA
Mean Glucose (mg/dL)	188 ± 12	166 ± 6	154 ± 4	144 ± 8	<0.001
Time >180 mg/dL	45% ± 6%	34% ± 3%	27% ± 2%	20% ± 5%	<0.001
Time <70 mg/dL	0.80% (0.37%, 1.01%)	1.67% (0.99%, 2.23%)	2.13% (1.21%, 2.90%)	1.66% (1.16%, 2.38%)	<0.001
HbA1c (%)	7.9 ± 0.8	7.3 ± 0.4	6.8 ± 0.4	6.5 ± 0.4	<0.001

Data are mean ± SD or median (IQR).
[a]Groups based on quartiles are for display only. Analysis was based on time-in-range 70–180 mg/dL as a continuous variable.
[b]Univariate *P*-values are from linear regression models with continuous time-in-range 70–180 mg/dL at follow-up as the dependent variable and the other glycemic measure as the predictor. *P*-values have been adjusted to control the false discovery rate.
CLC, closed-loop control; IQR, interquartile range; NA, not applicable; SD, standard deviation.

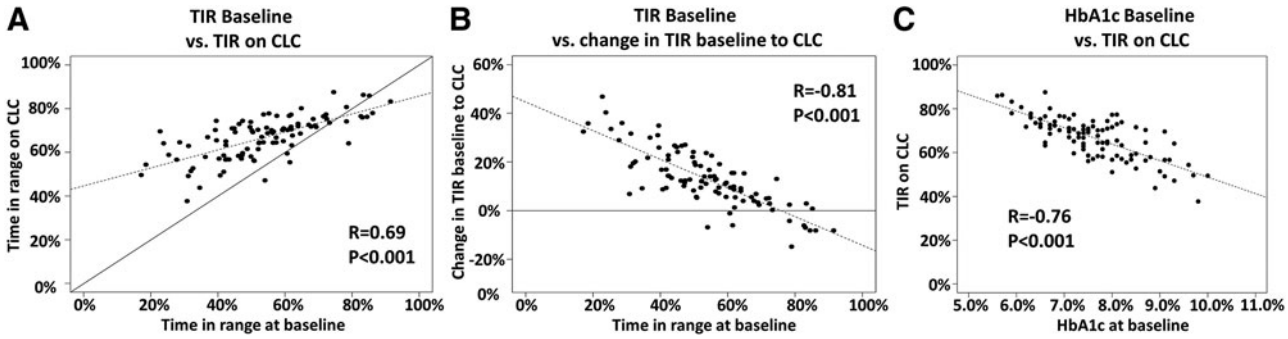

FIG. 2. Correlation between TIR at baseline, on CLC, and change in TIR between these periods. Correlations are provided for **(A)** TIR 70–180 mg/dL at baseline versus on CLC, **(B)** TIR at baseline versus change in TIR between baseline and on CLC, and **(C)** HbA1c baseline versus TIR on CLC. Dashed line represents the regression line; solid line represents the line of identity in **(A)** and no change in **(B)**.

Those with the lowest TIR on CLC had lower CGM use and closed-loop mode use (Table 2). In the lowest quartile, 36% participants were in closed-loop mode <90% of time compared to none in the highest quartile ($P < 0.001$).

In univariate analyses, children with lower TIR on CLC required greater amounts of daily insulin per kg ($P = 0.008$). The number of total boluses (user-initiated and automatic) per day was not associated with TIR on CLC ($P = 0.72$), with the lowest quartile receiving 11.8 ± 2.8 boluses per day compared to 12.0 ± 2.7 boluses per day for the highest quartile. However, in univariate analyses, lower TIR on CLC was associated with more automatic boluses (6.0 ± 1.6 vs. 3.5 ± 1.0 in the lowest and highest quartiles, respectively; $P < 0.001$), fewer user-initiated boluses (5.8 ± 2.6 vs. 8.5 ± 2.8; $P < 0.001$), fewer user-initiated boluses with carbohydrate entry (4.2 ± 2.0 vs. 5.8 ± 2.4; $P < 0.001$), and overall less total grams of carbohydrates entered each day (165 ± 67 vs. 206 ± 84; $P = 0.009$). There also was an association between the proportion of participants in each group receiving <3 boluses for carbohydrates per day and TIR (lowest TIR quartile 24%, highest TIR quartile 8%; $P = 0.01$).

After adjusting for baseline TIR in a multivariate model, user-initiated bolus doses and total daily insulin per kg were no longer significantly associated with TIR on CLC (Table 2).

Discussion

With the availability of two FDA-approved hybrid CLC systems for clinical use, attention is likely to shift from whether CLC systems improve glycemia in long-term use to how individual users can improve glycemic outcomes further while on a CLC system.

In this study of 12–16 weeks of use, we found that children who achieved greater TIR on the CLC system (compared to those with lower TIR) had more active involvement in their T1D management while on the system. This was evidenced by a greater number of user-initiated boluses, including more boluses for carbohydrate intake. However, these factors also were associated with baseline TIR before initiating CLC, and in a multivariate model, none of these factors remains significant after adjusting for baseline TIR. This suggests that even though CLC systems are designed to require less user input, individuals who are more attentive to administering boluses for carbohydrates, for example, are likely to achieve better outcomes.

It is notable that participants in the highest TIR quartile while using CLC already had good glycemic control at baseline, with 70% TIR and HbA1c of 6.8%—both of which nonetheless improved on the CLC system. While on CLC, this group initiated 2.7 noncarbohydrate boluses per day, suggesting that the participant or a family member continued to provide boluses for high blood glucose correction rather than rely on automated corrections, which are programmed to deliver 60% of the insulin calculated by the individual's correction factor and occur only if the most recent user-initiated bolus was delivered two or more hours prior. As such, these user-initiated correction boluses appeared to obviate the need for the CLC system to deliver automated boluses, which were lower overall in the highest versus lowest TIR quartile (3.5 vs. 6.0 daily).

Compared with those in the lowest TIR quartile, those in the highest TIR quartile also had greater time <70 mg/dL (1.66% vs. 0.80%), which was not significantly different from baseline (1.90% vs. 0.73%) and remains within the recommendation of <4% time <70 mg/dL.

The lowest TIR quartile while using CLC appeared to have omitted boluses of insulin for some amount of carbohydrate intake, delivering 4.2 boluses daily for a total of 165 grams compared with 5.8 boluses for a total of 206 g in the highest TIR group. The CLC system appeared, in part, to compensate for this by providing additional automated correction boluses (6.0 vs. 3.5 in the lowest vs. highest TIR group). Indeed, this CLC system has been shown to reduce hyperglycemia following unannounced carbohydrate ingestion, although not without some hyperglycemia excursion.[12] Of note, participants in the lowest TIR quartile using CLC required more insulin per body weight (1.13 vs. 0.87 U/kg/day in the highest TIR group), suggesting a greater amount of insulin resistance, although the reason for this in unclear. It is possible that increased exposure to hyperglycemia contributed to this increased insulin resistance.[13]

Although users with high TIR at baseline were able to achieve the highest TIR on CLC, those starting with a low TIR tended to improve the most. An analysis from the initial report of the RCT from the current study showed that individuals with baseline HbA1c ≥8.0% (compared with those with HbA1c <8.0%) experienced larger increases in TIR on

Table 2. Demographic, Clinical, and System Use Characteristics by Time-in-Range During Closed-Loop Control

	Time-in-range 70–180 mg/dL during CLC[b]					
	First quartile (n = 25)	*Second quartile (n = 25)*	*Third quartile (n = 25)*	*Forth quartile (n = 25)*	*Univariate, P*[c,e]	*Multivariate, P*[d,e]
Baseline glycemic measures						
Time-in-range 70–180 mg/dL	39% ± 11%	51% ± 12%	55% ± 11%	70% ± 14%	<0.001	<0.001
Baseline demographic and clinical characteristics						
Age (years)	11.4 ± 2.1	11.1 ± 2.0	10.8 ± 2.1	11.7 ± 1.9	0.83	0.08
Sex: female	15 (60%)	11 (44%)	9 (36%)	14 (56%)	0.76	0.03
Race/ethnicity: non-Hispanic White	20 (80%)	19 (76%)	22 (88%)	20 (80%)	0.75	0.48
Weight (kg)	46 ± 16	44 ± 16	40 ± 12	45 ± 13	0.50	N/A
BMI percentile	63 ± 30	63 ± 29	62 ± 27	60 ± 25	0.64	0.13
Duration of diabetes (years)	4.8 ± 2.6	6.5 ± 2.7	5.2 ± 2.9	4.6 ± 3.0	0.92	0.57
CGM user before baseline	22 (88%)	24 (96%)	23 (92%)	25 (100%)	0.02	0.13
Insulin pump before baseline	22 (88%)	18 (72%)	23 (92%)	21 (84%)	0.93	0.69
Detectable C-peptide[a]	8 (32%)	2 (8%)	7 (28%)	8 (32%)	0.37	0.06
Highest parent education					0.14	0.06
<Bachelor's degree	1 (4%)	3 (12%)	2 (8%)	2 (8%)		
Bachelor's degree	13 (52%)	13 (52%)	11 (44%)	4 (16%)		
≥Master's degree	11 (44%)	9 (36%)	12 (48%)	19 (76%)		
Annual household income					0.10	0.21
<$100,000	7 (32%)	10 (40%)	5 (22%)	5 (21%)		
$100,000–<$200,000	7 (32%)	7 (28%)	9 (39%)	12 (50%)		
≥$200,000	8 (36%)	8 (32%)	9 (39%)	7 (29%)		
CLC system use						
CGM use	96% (93%, 97%)	98% (96%, 98%)	96% (93%, 98%)	98% (97%, 98%)	0.001	NA
Closed-loop mode use	92% (88%, 93%)	94% (91%, 95%)	94% (91%, 96%)	94% (92%, 96%)	<0.001	0.13
Closed-loop mode use <90%	9 (36%)	4 (16%)	4 (16%)	0 (0%)	<0.001	NA
CLC system interaction						
Total daily insulin per kg	1.13 ± 0.27	0.95 ± 0.27	0.88 ± 0.27	0.87 ± 0.20	0.008	0.12
Total daily basal insulin per kg	0.55 ± 0.15	0.47 ± 0.13	0.37 ± 0.12	0.37 ± 0.11	<0.001	NA
Average insulin to carb ratio during the daytime (6 am–8 pm)	10.7 ± 6.3	13.7 ± 6.6	13.3 ± 5.5	11.8 ± 4.1	0.99	NA
Average insulin correction factor during the daytime (6 am–8 pm)	60 ± 42	77 ± 48	74 ± 41	67 ± 33	0.83	NA
No. bolus doses per day	11.8 ± 2.8	11.6 ± 2.5	11.3 ± 2.6	12.0 ± 2.7	0.72	NA
No. automatic bolus doses per day	6.0 ± 1.6	4.6 ± 1.7	4.0 ± 1.2	3.5 ± 1.0	<0.001	<0.001
No. user-initiated bolus doses per day	5.8 ± 2.6	6.9 ± 3.1	7.3 ± 2.6	8.5 ± 2.8	<0.001	0.46
No. user-initiated bolus doses with carb entry per day	4.2 ± 2.0	5.8 ± 3.0	6.0 ± 1.7	5.8 ± 2.4	<0.001	NA
No. user-initiated bolus doses with carb entry <3 per day	6 (24%)	2 (8%)	1 (4%)	2 (8%)	0.01	NA
Carbohydrate entered per day (g)	165 ± 67	199 ± 81	216 ± 70	206 ± 84	0.009	NA

Data are mean ± SD, median (IQR), or *n* (%).

[a]The detection limit of the assay was 0.003 nmol/L.

[b]Groups based on quartiles are for display only. Analysis was based on time-in-range 70–180 mg/dL as a continuous variable.

[c]Univariate *P*-values are from linear regression models with continuous time-in-range 70–180 mg/dL at follow-up as the dependent variable and the participant characteristics as the predictor.

[d]Multivariate *P*-values are from a single linear regression model with continuous time-in-range 70–180 mg/dL at follow-up as the dependent variable and the characteristics as predictors. To avoid multicollinearity, some factors were not included in the multivariate model. These variables are indicated by NA.

[e]*P*-values have been adjusted to control the false discovery rate.

BMI, body mass index; CGM, continuous glucose monitoring; CLC, closed-loop control.

CLC (19.5% vs. 10.8%), also reflective of their having had lower TIR at baseline (41% vs. 60%).[9] This remains an important consideration regarding which patients may benefit the most from a CLC system.

Our study benefited from a large cohort with only 1% drop-out. Limitations include the composition of the cohort, which was overall well controlled, with mean baseline HbA1c values below 8% for each of the quartiles. This may limit the generalizability of the findings from this study, particularly given that the T1D exchange reported that mean HbA1c nationally in this age range was 8.5%.[1] In addition, the families represented were relatively affluent and well-educated, with 70% of families having a yearly income >$100,000 and 45% of families having at least a Master's degree.

Additional limitations of the current analysis include its observational nature; therefore, some of the differences we observed between TIR quartiles may have merely been associations and not causative of the variation in TIR. In addition, we lack information on the true amount of carbohydrates consumed, limiting our ability to understand the impact of the differences in the amount of carbohydrates entered and the number of boluses between groups. Finally, this analysis combined baseline data of variable durations, although CGM metrics were similar between groups as previously published.[9]

In conclusion, we found that among children 6–14 years old who used the Control-IQ hybrid CLC system for up to 16 weeks in a clinical trial, TIR was most closely linked to baseline glycemic control and to the degree of engagement of the family with the system. Those with the lowest TIR at baseline were the ones who improved TIR the most, but ultimately those with the highest TIR at baseline were those who had the highest TIR on CLC. The data on system engagement serve as a reminder that hybrid CLC systems are likely to provide greater TIR with greater user interaction, including user-initiated boluses for carbohydrate intake and correction of elevated blood sugar. Further observational studies will be instructive regarding TIR achievements among cohorts with poorer baseline control and lower system engagement.

Authors' Contributions

M.J.S. and M.D.D. developed the concept for the article. L.G.K. analyzed the data. M.J.S., L.G.K., and M.D.D. wrote the article. All authors were responsible for reviewing and revising this article and assume responsibility and accountability for the results.

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Author Disclosure Statement

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