Outpatient Closed-Loop Control with Unannounced Moderate Exercise in Adolescents Using Zone Model Predictive Control

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Abstract

Background: The artificial pancreas (AP) has the potential to improve glycemic control in adolescents. This article presents the first evaluation in adolescents of the Zone Model Predictive Control and Health Monitoring System (ZMPC+HMS) AP algorithms, and their first evaluation in a supervised outpatient setting with frequent exercise.

Materials and Methods: Adolescents with type 1 diabetes underwent 3 days of closed-loop control (CLC) in a hotel setting with the ZMPC+HMS algorithms on the Diabetes Assistant platform. Subjects engaged in twice-daily exercise, including soccer, tennis, and bicycling. Meal size (unrestricted) was estimated and entered into the system by subjects to trigger a bolus, but exercise was not announced.

Results: Ten adolescents (11.9–17.7 years) completed 72 h of CLC, with data on 95 ± 14 h of sensor-augmented pump (SAP) therapy before CLC as a comparison to usual therapy. The percentage of time with continuous glucose monitor (CGM) 70–180 mg/dL was $71\% \pm 10\%$ during CLC, compared to $57\% \pm 16\%$ during SAP ($P=0.012$). Nocturnal control during CLC was safe, with 0% (0%, 0.6%) of time with CGM <70 mg/dL compared to 1.1% (0.0%, 14%) during SAP. Despite large meals (estimated up to 120 g carbohydrate), only $8.0\% \pm 6.9\%$ of time during CLC was spent with CGM >250 mg/dL ($16\% \pm 14\%$ during SAP). The system remained connected in CLC for $97\% \pm 2\%$ of the total study time. No adverse events or severe hypoglycemia occurred.

Conclusions: The use of the ZMPC+HMS algorithms is feasible in the adolescent outpatient environment and achieved significantly more time in the desired glycemic range than SAP in the face of unannounced exercise and large announced meal challenges.

Keywords: Adolescent, Algorithms, Artificial pancreas, Exercise, Type 1 diabetes.

Introduction

ADVANCES IN MEDICAL device technology have enabled vast improvements in the way that type 1 diabetes (T1D) is treated. For example, the use of continuous glucose monitors (CGMs) provides patients with a wealth of information

about their blood glucose (BG) concentration, its history, and its real-time trends, allowing them to make more informed adjustments to their insulin therapy. In addition to CGMs, rapid-acting insulins and programmable pumps for continuous subcutaneous insulin infusion (CSII) have also shown promise in allowing patients to exert finer control over their

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BG; however, successful implementation of CSII and CGMs requires time, effort, and ongoing education on the part of patients and their families.¹ The development of a closed-loop artificial pancreas (AP) device to regulate the BG by adjusting insulin delivery in real time based on feedback from a CGM will automate the treatment process, removing much of the daily patient effort and active decision-making that are a part of manual treatment.²

Model predictive control (MPC) is an advanced control strategy that has been widely implemented in the chemical industry for controlling complex processes with input and output constraints.^{3,4} This control strategy is promising for use in the AP, especially due to its ability to directly incorporate physiological constraints (i.e., cannot remove insulin from the body), its capacity to handle delays in insulin action, and its customizability in designing the objective function to optimize insulin delivery according to clinical needs.^{5,6} The Zone MPC (ZMPC) AP algorithm uses a model to predict the future BG trajectory and calculates the optimal insulin dose needed to maintain the BG trajectory within a desired zone, rather than at a specific set point.^{6–8} When the BG is predicted to be within the desired zone, the controller delivers the usual basal insulin dose to minimize excessive controller action in response to small changes in CGM measurements, such as may occur with sensor noise. When the predicted BG trajectory includes excursions from the zone, the controller modulates the insulin dose to deliver the optimal dose with respect to the objective function. The Health Monitoring System (HMS) provides a safety layer, independent of the controller, to predict and alert the user to impending hypoglycemia.⁹

The ZMPC algorithm has performed well in several controlled inpatient and research suite evaluations in adults with T1D.^{5,10,11} For this controller to be tested in the outpatient setting, a portable platform is required. To this end, the ZMPC+HMS algorithms were integrated into the Diabetes Assistant (DiAs) platform from the University of Virginia (UVA), hosted on an Android smartphone,¹² which has now been used in multiple outpatient trials.^{13–15} The DiAs system has undergone extensive clinical testing to demonstrate its safety and feasibility for use in the outpatient setting.¹² The remaining components of the AP system are a Dexcom G4 Share AP CGM and a Roche Accu-Chek Spirit Combo CSII pump. The devices communicate wirelessly with the DiAs system/smartphone through Bluetooth, eliminating the need for hard-wired connections. The data are automatically transferred by the DiAs platform to a secured server to allow the user's status to be monitored remotely.

While the feasibility of the AP with ZMPC+HMS has been demonstrated in the adult population in controlled inpatient or research suite settings, it has neither been evaluated in children or adolescents nor in highly ambulatory settings with frequent exercise.^{5,10} Satisfactory glucose control in adolescents and children with T1D is notoriously difficult to achieve, with T1D Exchange data showing that ~80% of adolescents have hemoglobin A1c (HbA1c) values above the American Diabetes Association target of 7.5% (58 mmol/mol).^{16,17} This trend is particularly concerning for older adolescents, who saw an average HbA1c of 9.0% (75 mmol/mol) in the 13- to 17-year-old age group.¹⁷ Adolescents experience both physiological challenges due to changes in insulin sensitivity related to puberty^{18–21} and psychosocial barriers presenting as missed meal boluses, less frequent self-

monitoring of blood glucose (SMBG) testing, and difficulty following a fixed plan or regimen.²² A significantly elevated insulin resistance in pubertal teenagers presents a challenge to model-based controllers, as the parameters for this population may differ from those modeled for adults with T1D. Additional challenges to AP systems in this age group include school-based sports and more frequently missed meal boluses.

The purpose of this study was to determine the feasibility of the AP with ZMPC+HMS in adolescents with T1D engaging in supervised, free-living conditions with twice-daily mild-to-moderate intensity exercise. This study represents the first evaluation of the ZMPC+HMS algorithms in the adolescent population. In addition, this study is the first evaluation of the ZMPC+HMS algorithms in the transitional hotel environment with frequent repeated exercise, thus bridging the gap between the inpatient and unsupervised outpatient settings.

Research Design and Methods

ZMPC+HMS/DiAs system

The integration of the ZMPC+HMS algorithms with the DiAs platform and devices comprises a portable automated glucose management system (Supplementary Fig. S1; Supplementary Data are available online at www.liebertpub.com/dia). The ZMPC algorithm automatically commands the insulin dose based on current and historical CGM measurements, predicted BG trends, historical insulin delivery, the time of day, and patient-specific information. The model of insulin-BG dynamics used by the controller to characterize the future BG trajectory is personalized using the subject's total daily insulin (TDI) dose. The algorithm is designed to drive the BG to a target zone. During the day (06:00–22:00), the target zone is 80–140 mg/dL and during the night (24:00–04:00), the target zone is 90–140 mg/dL, with smooth 2-h transitions in between. As long as the BG is predicted to remain in the target zone, the controller delivers the subject's basal rate. The ZMPC algorithm is described in detail in Gondhalekar *et al.*²³

The HMS provides a safety layer outside the ZMPC algorithm by analyzing CGM data and trends to detect impending hypoglycemia.⁹ This system produces an audio-visual alarm when the BG is predicted to cross the 65 mg/dL threshold within 15 min. The user is prompted to perform an SMBG measurement and treat with oral carbohydrates (CHO), thus preventing or mitigating the impending hypoglycemic episode.

The ZMPC+HMS/DiAs system is programmed at the start of the study with the user's TDI dose, as well as the insulin to CHO ratio (CR), correction factor (CF), and basal rate profiles. Meal announcements are made through the DiAs interface to trigger a bolus. The bolus size is computed using the preprogrammed CR and CF profiles based on the meal size estimate and an SMBG measurement. If the SMBG at the time of the meal is <120 mg/dL or if no SMBG is entered, the bolus size is 80% of the value computed using the CR. If the SMBG at the time of the meal is >120 mg/dL, the bolus size is 100% of the value computed using the CR. If the SMBG is >150 mg/dL, the full meal bolus is accompanied by a correction bolus to 150 mg/dL calculated using the CF. The correction bolus is added only if there has not been another meal bolus with a correction bolus within the past 2 h. The correction bolus is limited to a maximum of 2 U.

The insulin dose calculated by the controller is subject to safety constraints. At each 5-min interval, the insulin dose is limited to a maximum of 1 U (excluding meal/correction boluses). During the period 22:00–04:00, the insulin infusion is constrained to be <1.8 times the basal rate. Finally, the Insulin on Board (IOB) constraint prevents overdelivery of insulin by taking into account the insulin infusion history over the past 8 h.^{23,24}

Study design

The primary objective of this study was to determine safe and feasible operation of the ZMPC+HMS/DiAs system in adolescents with T1D engaging in free-living conditions with twice-daily unannounced mild-to-moderate intensity exercise. Ten subjects were recruited for the study (five subjects each at Stanford University [SU] and the Barbara Davis Center [BDC]). Subjects resided in a hotel setting for 3 days, where they slept overnight and engaged in mild-to-moderate intensity exercise at least twice daily, with clinical staff in attendance at all times. To emulate free-living conditions, subjects chose the size, content, and timing of their meals, with no restriction on meal size. The study protocol was approved by the SU Institutional Review Board, the Colorado Multiple Institutional Review Board, and the FDA, and was registered on Clinicaltrials.gov (NCT02506764).

The inclusion criteria for the study were as follows: clinical diagnosis of T1D, daily insulin therapy for at least 12 months, aged 10–19 years, insulin pump use for at least 3 months with current use of a downloadable pump, TDI dose requirement >0.4 U/(kg·day) over the preceding 2 weeks, and ability to speak and understand English. Additional criteria for female participants were as follows: use of acceptable method of contraception if sexually active and a negative urine pregnancy test for subjects who have entered menarche. Informed consent was obtained from subjects and/or parents and the assent form signed by the subject if <18 years. Study exclusion criteria were diabetic ketoacidosis (DKA) in the past month, history of seizure or loss of consciousness in the last 6 months, or any medical disorder that would affect the completion of the protocol.

Study preparation

The Dexcom G4 Share CGM was inserted during a screening visit at least 72 h before the hotel admission. In this study, subjects wore their CGM sensor beyond the standard approved time of 1 week if it was still working, to mimic real-world use and determine if we could predict sensor failures. Subjects continued with their usual sensor-augmented pump (SAP) therapy during the period between CGM insertion and the beginning of the closed-loop control (CLC) phase. The data from this period were analyzed to determine the subjects' usual glycemic control. Upon arrival for the CLC phase, subjects removed their own pumps and inserted a new infusion set for use with the study pump. After programming the pump and DiAs system with the subjects' information and establishing communication between the study devices, CLC was commenced. Each subject was provided with either an Accu-Chek Aviva Connect or a Bayer Contour NEXT blood glucose meter to take SMBG measurements as needed throughout the study.

Daily study procedures

A full timeline of events at each site is shown in Supplementary Figure S2. The daily procedures for the trial were as follows: subjects ate breakfast at the hotel and then left for supervised sessions of physical activity in the morning and afternoon. The physical activity sessions consisted of mild-to-moderate intensity exercise of variable duration lasting at least 30 min. The exercise sessions included activities such as soccer, basketball, tennis, ultimate Frisbee™, walking, and bicycling. Exercise was not announced to the AP system. Lunch was provided during the afternoon between physical activity sessions. Dinner was consumed in the evening, followed by additional activities such as playing pool, completing schoolwork, and watching movies. CLC continued for 3 full days (72 h). Throughout the study, subjects made their own food choices and decided their own meal size announcement. At least three meals were consumed per day, with no restrictions on food selection. Subjects were also free to choose the type and intensity of physical activity.

Participants were provided with a meter and test strips for fingerstick SMBG measurements. SMBG measurements were required at a minimum of five times daily (before meals, before and after exercise, and at bedtime) throughout the study. An additional SMBG check was performed by study staff at 03:00. CGMs were calibrated as per the manufacturer's instructions (at least twice daily) and any time there was a calibration request from the CGM itself, provided that the SMBG was between 40 and 400 mg/dL and the CGM indicated a low rate of change (ROC) by displaying a horizontal arrow. The CGM was also calibrated if the difference compared to SMBG was $>20\%$.

Safety and remote monitoring

At least one clinical staff member was present at all times to supervise use of the system. Monitoring was performed either by visually observing the subjects or by checking the remote monitoring website to view the current status of all subjects. Subjects were asked to respond to HMS alerts predicting that glucose levels would drop to below 65 mg/dL in the next 15 min by taking an SMBG measurement. The HMS alert prompted the user to enter the SMBG and indicate whether treatment was given. In the case that $\text{SMBG} \geq 70$ mg/dL, the subject was prompted to treat with 15 g oral CHO, but the treatment was not required. In the case that $\text{SMBG} < 70$ mg/dL or the subject was symptomatic, the subject was given 15 g oral CHO and the SMBG check and treatment process were repeated every 15 min until $\text{SMBG} > 70$ mg/dL and/or the subject was no longer symptomatic.

Statistical methods

The primary outcome of this study was the feasibility of the system in this cohort and setting. Feasibility was defined as proper functioning of the system for at least 75% of the total study time. Secondary outcomes included percentage of time spent in various glycemic ranges and mean CGM (as described in the recommendations published in Maahs et al.²⁵). The secondary outcomes were evaluated using CGM values from the entire CLC period. The data are presented as either mean $\pm$ standard deviation (SD) or median (interquartile range [IQR]), depending on the determined

TABLE 1. SUBJECT DEMOGRAPHICS (N=10)

<i>Characteristics</i>	
Age, years, mean $\pm$ SD (range)	15.3 $\pm$ 1.8 (11.9–17.7)
Gender, <i>n</i> (%)	
Female	5 (50)
Male	5 (50)
Race and ethnicity, <i>n</i>	
White	9
Native Hawaiian or Pacific Islander	1
Weight, kg, mean $\pm$ SD (range)	58.4 $\pm$ 13.9 (37.4–85.2)
Body mass index, kg/m ² , mean $\pm$ SD (range)	21.5 $\pm$ 3.6 (15.6–26.9)
HbA1c	
%, mean $\pm$ SD (range)	8.1 $\pm$ 1.3 (6.8–11.2)
mmol/mol, mean $\pm$ SD (range)	65 $\pm$ 14 (51–99)
Duration of diabetes, years, mean $\pm$ SD (range)	5.1 $\pm$ 2.3 (2.3–9.6)
TDI	
U/day, mean $\pm$ SD (range)	49 $\pm$ 18 (27–86)
U/(kg $\cdot$ day), mean $\pm$ SD (range)	0.82 $\pm$ 0.17 (0.60–1.14)

HbA1c, hemoglobin A1c; SD, standard deviation; TDI, total daily insulin.

distribution. Comparison between the CLC and SAP data was performed using either a paired sample Student's *t*-test for normally distributed data or the Wilcoxon signed-rank test for nonnormal data. Normality was determined using the Shapiro-Wilk goodness-of-fit test. The statistical analysis was performed using Matlab 2015b.

Results

Ten adolescents (11.9–17.7 years, 5 M/5 F) completed 3 days of CLC in a hotel setting, resulting in 30 person-days of CLC. Subject information is shown in Table 1. Data from 95 $\pm$ 14 h of SAP immediately before CLC are included to provide a comparison to the subjects' glycemic control with their usual therapy.

System performance

The system demonstrated feasibility in this cohort, with CLC active for 95.0% $\pm$ 1.1% of the intended study time or 97.3% $\pm$ 1.7% of the time when excluding the 2 h of disconnection resulting from CGM reset and warm-up required in 5 of the 10 subjects after the first 7 days of sensor wear, and 1 subject who had to replace the CGM sensor the last night of the study. The primary cause of time spent out of CLC was disruption in the Bluetooth connection between the devices. The system was safe in this cohort, with no episodes of DKA or severe hypoglycemia resulting in seizure or coma. The HMS performed as designed and the system provided hypoglycemia alerts as expected.

In one subject (referred to as subject 4), the controller did not perform as intended due to a technical issue with the integration of the DiAs and ZMPC systems. Due to a timing anomaly, the controller did not exploit CGM feedback properly for $\sim$ 60% of the study duration. During this time, the controller was not able to respond as designed to in-

creasing or decreasing CGM trends. Instead, basal insulin delivery was commanded. The issue was not detected until the data analysis stage of the study and did not affect safety during the trial. The subject's data were included in the analysis on an intention-to-treat basis for the feasibility and glucose control endpoints; however, the subject is delineated from the others during discussions of controller performance.

Glucose control

The glycemic control characteristics during CLC and SAP are summarized in Table 2 and Figure 1. Overall, subjects spent 71% $\pm$ 10% of time in the desired range of 70–180 mg/dL. The CLC period showed a significant improvement over the subjects' usual SAP therapy, where only 57% $\pm$ 16% of time was spent in the 70–180 mg/dL range ($P=0.012$). In addition, time in the tight control range of 80–140 mg/dL was significantly longer during the CLC session, with 47% (39%, 53%) of time in range during CLC, compared to 30% (21%, 42%) during SAP ($P=0.002$). In general, CLC provided a tighter distribution of CGM values, with a narrower vertical band on the cumulative histogram (Supplementary Fig. S3).

The mean CGM during CLC was 150 $\pm$ 19 mg/dL. This result was significantly lower than the SAP value of 173 $\pm$

TABLE 2. COMPARISON OF GLYCEMIC CONTROL FOR CLOSED-LOOP CONTROL VERSUS SENSOR-AUGMENTED PUMP IN 10 ADOLESCENT SUBJECTS USING SENSOR-AUGMENTED PUMP AT HOME FOR $\sim$ 4 DAYS, THEN FOLLOWED BY CLOSED-LOOP CONTROL IN A FREE-LIVING, SUPERVISED ENVIRONMENT FOR 3 DAYS

	CLC	SAP	P-value
Day and night			
Mean CGM (mg/dL)	150 $\pm$ 19	173 $\pm$ 31	0.042*
SD CGM (mg/dL)	58 $\pm$ 13	95 $\pm$ 14	0.23
COV CGM (%)	39 $\pm$ 5	38 $\pm$ 8	0.87
Percent of time CGM			
70–180 mg/dL	71 $\pm$ 10	57 $\pm$ 16	0.012*
80–140 mg/dL	47 (39, 53)	30 (21, 42)	0.002*
>180 mg/dL	26 $\pm$ 11	39 $\pm$ 18	0.033*
>250 mg/dL	8.0 $\pm$ 6.9	16 $\pm$ 14	0.088
>300 mg/dL	3.5 $\pm$ 3.9	7 $\pm$ 7.6	0.220
<70 mg/dL	2.5 $\pm$ 0.8	4.2 $\pm$ 3.1	0.130
<60 mg/dL	0.68 $\pm$ 0.63	1.9 $\pm$ 1.8	0.076
<50 mg/dL	0.13 $\pm$ 0.26	0.44 $\pm$ 0.5	0.125
Overnight (00:00–07:00)			
Mean CGM (mg/dL)	154 $\pm$ 30	157 $\pm$ 45	0.832
SD CGM (mg/dL)	45 $\pm$ 6	46 $\pm$ 19	0.91
COV CGM (%)	29 $\pm$ 8	30 $\pm$ 9	0.88
Percent of time CGM			
70–180 mg/dL	71 $\pm$ 22.5	67 $\pm$ 23	0.713
80–140 mg/dL	46 $\pm$ 26	34 $\pm$ 17	0.180
>180 mg/dL	29 $\pm$ 23	27 $\pm$ 28	0.902
>250 mg/dL	6 $\pm$ 7.1	11 $\pm$ 18	0.456
>300 mg/dL	2.2 $\pm$ 3.8	4.2 $\pm$ 7.1	0.448
<70 mg/dL	0 (0, 0.6)	1.1 (0, 14)	0.078
<60 mg/dL	0 (0, 0.2)	0.1 (0, 7.6)	0.156
<50 mg/dL	0 (0, 0)	0 (0, 1.5)	0.250

* P -value <0.05.

CGM, continuous glucose monitor; CLC, closed-loop control; COV, coefficient of variation; SAP, sensor-augmented pump.

FIG. 1. Box and whisker plot showing the percentage of time with CGM in various ranges during SAP (white) and CLC (shaded). The horizontal lines indicate the medians, the box represents the IQR, and the thin vertical lines represent the range. Outliers are depicted using plus symbols. The top plot shows 24-h control and the bottom plot shows overnight control (00:00–07:00). CGM, continuous glucose monitor; CLC, closed-loop control; IQR, interquartile range; SAP, sensor-augmented pump; TIR, time in range.

31 mg/dL ($P=0.042$). Excluding subject 4, subjects who had a high mean CGM (>168 mg/dL) during SAP saw a decrease to a lower value during CLC, along with an increase in the percent time with CGM 70–180 mg/dL. For other subjects, the mean CGM remained steady, while the percentage of time in hypoglycemia remained similar or decreased (Fig. 2A).

The median and IQR CGM traces for 24-h glycemic control for CLC and SAP are shown in Figure 3. The distribution of announced meals and snacks during CLC is shown in the lower panel of the figure (meal information was not recorded during SAP). Several dinner meals were consumed late in the evening (19:49, 20:53, and 20:11), which contributed to the hyperglycemia in the beginning of the overnight period experienced by some subjects. Individual glucose and insulin traces for each subject are shown in the Supplementary Data.

Hypoglycemia

Time spent with CGM <70 mg/dL was $2.5\% \pm 1.8\%$ during CLC. While this result is less than the SAP value of $4.2\% \pm 3.1\%$, the difference was not significant ($P=0.13$).

Overnight (00:00–07:00), time <70 mg/dL during CLC was reduced to 0% (0%, 0.6%). The amount of time spent in hypoglycemia as defined by various thresholds during CLC and SAP is shown in Table 2 and Supplementary Figure S4. Information about the number and duration of hypoglycemic episodes during CLC (defined as a CGM excursion below the specified threshold for >10 min as recommended in Maahs et al.²⁵) is shown in Table 3. Overall, there were 1.3 (0.58, 2.0) episodes/(subject·day) <70 mg/dL and 0.33 (0.0, 0.5) episodes/(subject·day) <60 mg/dL. The HMS provided 1.8 (1.3, 3.5) alarms/(subject·day) warning of impending hypoglycemia. These alerts allowed subjects to take a CHO treatment before the hypoglycemic event began, thereby preventing or shortening the impending event.

Three subjects each experienced a single event where the CGM measured below 50 mg/dL. These events lasted 4, 24, and 25 min, respectively. They were preceded by 124, 72, and 48 min of pump suspension, which started when the CGMs were 133, 168, and 110 mg/dL. The second event occurred during exercise, although the CGM was already at 87 mg/dL when exercise began. Alerts from the HMS and corresponding CHO treatments, as well as the controller-directed suspension of insulin delivery, allowed subjects to recover quickly from these episodes, with no adverse events. Each of these events occurred in the time period 2–4 h after a meal, indicating that the meal bolus could have contributed to the event.

Insulin

The average TDI dose during CLC was 47 ± 18 U/day [0.81 ± 0.24 U/(kg·day)]. This amount was not significantly different from the subjects' usual TDI dose of 49 ± 18 U/day [0.82 ± 0.17 U/(kg·day)] ($P=0.62$). Still, the percentage of time spent in hyperglycemia (>180 mg/dL) decreased from $39\% \pm 18\%$ of time during SAP to $26\% \pm 11\%$ of time during CLC ($P=0.03$). The ZMPC+HMS system was able to significantly reduce the amount of time spent in hyperglycemia without significantly increasing the TDI dose or increasing time spent in hypoglycemia.

Carbohydrate consumption

Meal choice throughout the study was determined by the subjects, with no restrictions. The average amount of CHO estimated for meals per day was 208 ± 32 g for female subjects ($n=5$, mean weight 56 kg) and 259 ± 60 g for male subjects ($n=5$, mean weight 61 kg). Meal size estimation and announcement were performed by subjects. A standard schedule of three daily meals was followed, with opportunities for snacks as desired.

Exercise

Subjects engaged in two to three daily sessions of mild-to-moderate intensity exercise lasting at least 30 min each. This frequency and duration of exercise were intended to challenge the system, since there was no announcement to the controller of exercise or preexercise preparation, such as lowering or suspending basal insulin delivery. In addition, exercise took place in the period of 1–3 h following large breakfast or lunch meals, when the IOB could be high (estimated IOB at start of exercise was 2.0 U [0.54 , 4.1 U]).

FIG. 2. Summary of glycemic control during CLC. **(A)** Mean CGM for each subject during SAP and CLC (connecting line represents same subject). The size of the circle icon indicates the percentage of time spent below 70 mg/dL. The dashed horizontal line in **(A)** represents a mean CGM of 168 mg/dL, which corresponds to an HbA1c of 7.5% (58 mmol/mol).³⁵ **(B)** CGM at exercise end (CGM_{end}) versus minimum rate of change during exercise (ROC_{min}) for each exercise period and for each subject. The size of the icon indicates the length of pump suspension associated with that exercise period, in minutes. Exercise periods with no pump suspension are filled black. Exercise periods with no pump suspension for subject 4 are displayed as an asterisk symbol. HbA1c, hemoglobin A1c; ROC_{min}, minimum rate of change.

Since there was no exercise announcement or activity measurement in this study, the only way for the controller to react to an exercise event was through feedback from the CGM (i.e., if the CGM decreases quickly or approaches hypoglycemia). In Figure 2B, the CGM at exercise end (CGM_{end}) is plotted versus the minimum rate of change (ROC_{min}) during each exercise session, with the size of the icon indicating the duration of any associated controller-

directed pump suspension. There are three ways a pump suspension can be associated with an exercise period: (1) the pump suspension began during the exercise period, (2) the pump suspension began before the exercise period and lasted at least 30 min after the start of the exercise period, or (3) the pump suspension began within 30 min of the end of the exercise period. An indication of desired controller performance is a pump suspension when CGM_{end} is low, especially

FIG. 3. CGM over 24 h during SAP and CLC periods. The solid and dashed lines show the median CGM trace for 10 subjects for CLC and SAP, respectively. The IQR during CLC is represented by the dark shaded region, and the IQR during SAP is represented by the striped region. The lower panel shows the time and size of announced meals during CLC (meal information was not recorded during SAP).

TABLE 3. SUMMARY OF HYPOGLYCEMIC EPISODES LASTING MORE THAN 10 MIN BY CONTINUOUS GLUCOSE MONITOR

	<50 mg/dL	<60 mg/dL	<70 mg/dL
Day and night			
Total episodes	2	11	36
Per subject per day	0 (0, 0.08)	0.33 (0, 0.5)	1.3 (0.58, 2.0)
Exercise (+30 min)			
Total episodes	1	7	18
Per subject per day	0 (0, 0)	0.17 (0, 0.42)	0.5 (0.33, 1.0)
Overnight (00:00–07:00)			
Total episodes	0	2	3
Per subject per day	0 (0, 0)	0 (0, 0)	0 (0, 0.08)

Episodes are delineated by day and night control, during and 30 min after exercise and during the overnight period, shown as median (IQR).

IQR, interquartile range.

if the CGM was decreasing quickly. In addition, the pump should not be suspended (or should suspend for only a short period) if CGM_{end} is high and/or if the CGM was steady or increasing.

As shown in Figure 2B, the controller performed as desired during exercise in this study. Excluding subject 4, there were pump suspensions associated with all exercise periods with $\text{CGM}_{\text{end}} < 108 \text{ mg/dL}$, regardless of the ROC_{min} . If the CGM during exercise decreased any faster than $0.9 \text{ mg}/(\text{dL} \cdot \text{min})$, then there were pump suspensions for all exercise periods with $\text{CGM}_{\text{end}} < 131 \text{ mg/dL}$. If the CGM decreased at a rate higher than $1.6 \text{ mg}/(\text{dL} \cdot \text{min})$, there were pump suspensions for all exercise periods, regardless of CGM_{end} . Finally, the pump did not suspend for each exercise period with ROC_{min} greater than $-0.9 \text{ mg}/(\text{dL} \cdot \text{min})$ and $\text{CGM}_{\text{end}} > 150 \text{ mg/dL}$. Including subject 4, there were three instances where a pump suspension would have been desired, but did not occur. These results are summarized in Supplementary Table S1. As a result of the ZMPC+HMS action during exercise, only $1.5^{1,3}$ exercise sessions per subject (of a total 6 or 7 exercise sessions) resulted in a hypoglycemic event with $\text{CGM} < 70 \text{ mg/dL}$.

Discussion

In this article, we present the first evaluation of ZMPC+HMS in the adolescent population performing multiple unannounced exercise sessions in a supervised camp environment. This study showed that the use of this system is feasible in this population. Even in the face of challenges such as large free-choice meals, twice-daily mild-to-moderate unannounced exercise, and ambulatory conditions in the outpatient environment, the controller was able to achieve $71\% \pm 10\%$ time in range, which is an improvement over the subjects' typical control ($57\% \pm 16\%$ time in range). This improvement was made without increasing the amount of time spent in hypoglycemia or increasing the TDI dose.

The glycemic control in this study is comparable to that observed in other day-and-night studies of CLC for adolescents. For example, Tauschmann et al.²⁶ showed a median

(IQR) of 72% (59%, 77%) of time spent with CGM between 70 and 180 mg/dL, compared to our study, which had 72% (64%, 79%) time in this range. Similarly, Ly et al.²⁷ reported a mean of 70% time spent in the same range. In a later study, Ly et al.²⁸ report a 13% improvement in time in target glucose range at a summer camp, similar to our results where we showed a 14% improvement in time, 70–180 mg/dL. While the protocols and controller designs of these studies differed, the similarity of the results for insulin-only systems indicates that performance may be limited by the constraints of the slow action of subcutaneous insulin and the hormones present during adolescence that make glycemic control difficult. In addition, these systems are not fully automated. There is work involved for the patients that can introduce error into the system, such as in meal size estimation and determination of basal, CR, and CR profiles. Innovations in AP design to reduce the need for patient interaction, including faster insulin action, may be needed to improve above the 70%–75% time-in-range mark.

The pattern of hypoglycemic episodes during the postprandial period, especially visible following breakfast (Fig. 3), suggests that some of the meal boluses may have been too large, especially when coupled with exercise following the meal. Subjects performed two to three daily sessions of mild-to-moderate intensity exercise lasting at least 30 min each, 1–3 h after the breakfast or lunch meal, without any exercise announcement or adjustment in basal rates before exercise. The amount of time spent on exercise activities was $\sim 3 \text{ h}/(\text{subject} \cdot \text{day})$. Subjects also did not reduce their preexercise meal boluses, as is often recommended.^{29,30} Despite these challenges, there were still low rates of hypoglycemia, attesting to the robustness of the controller function.

Although the system is designed to give 80% of the total meal bolus when SMBG is below 120 mg/dL, there were 57 out of 161 meals that were announced with SMBG $> 120 \text{ mg/dL}$ and therefore received the full bolus. One potential cause of postprandial hypoglycemia is a CR that is too high. An algorithmic adjustment of the CR based on open-loop data as in Dassau et al.¹⁰ could potentially reduce postprandial hypoglycemia during CLC. Errors in the estimation of the meal size could be caused either by subjects estimating CHO for the entire meal, but only consuming part of it, or overestimating the amount of CHO in the meal. Subject behavior could also be influenced by the clinician-supervised setting, where there may be more pressure to demonstrate good control and avoid underdosing. Several studies have investigated the use of a partial bolus based on a percentage of the total calculated bolus for the meal regardless of the SMBG, allowing the controller to deliver the rest of the required insulin on an as-needed basis using feedback from the CGM.^{31–33} While Elleri et al.³⁴ did not find evidence that a partial meal bolus reduced the risk of hypoglycemia, they found that it did not decrease the time spent in range (70–180 mg/dL). Further investigation is needed to optimize the integration of an announced meal bolus within the AP system.

There was some hyperglycemia during the overnight period in this study, especially in the first half of the night. This hyperglycemia was caused by late-night meals and snacking, as shown in the lower panel of Figure 3. The protocol should always be consulted when interpreting overnight control

results calculated using a common predetermined time range (e.g., 00:00–07:00), especially for studies that allow varying, or unusual, meal and sleep schedules. Protocols that allow late-night meals or snacks inevitably result in more overnight hyperglycemia. Overnight control in this study was conservative by design, with tightened safety constraints in place 22:00–06:00 to prevent overdelivery of insulin during times of sleep. Using fixed start and end times for the additional safety measures at night does not allow for flexible or atypical schedules. Our design prioritized safety overnight, and the controller action may have been limited in some cases due to high IOB from frequent snacks, including several large after-dinner snacks eaten late at night. An added announcement for sleep, to start the safety constraints, may reduce overnight hyperglycemia if users are awake and/or eating at atypical times. However, this extra announcement requires additional work by the user and may lead to safety risks if the user forgets to make the announcement. The compromise between design safety and efficacy is an important consideration as the AP moves forward.

We recognize there were several limitations in this study. There was a small sample size of 10 subjects and the study was not randomized. In addition, although this study took place in the outpatient environment, subjects were supervised at all times to ensure safety during CLC. They were not supervised during SAP use and may not have performed the same frequency of exercise as they did while on CLC. Study staff was on hand to assist subjects with troubleshooting the system, checking infusion sets and CGM sites, and responding to system alerts. However, subjects were responsible for estimating and entering meal size, taking SMBG measurements, and otherwise interacting with the DiAs interface. The presence of the clinical team ensured that HMS and other system alarms were responded to promptly. The level of supervision in this study, necessary to comply with regulatory requirements, had the advantage of ensuring the best possible assessment of the ZMPC algorithm itself, with minimal time spent out of CLC and no confounding factors related to patient noncompliance.

Some technical difficulties were encountered during this study. These issues represent the primary challenge that is faced when transitioning from a highly controlled inpatient environment to a more unpredictable outpatient environment. A timing anomaly between the CGM and the DiAs system caused a malfunction in the controller for one subject, resulting in suboptimal (but still safe-by-design) performance. The potential for this issue has since been addressed in updated versions of the system. In addition, disruptions in the Bluetooth communication between the pump, CGM, and DiAs system resulted in some time spent out of CLC. These communication problems will be eliminated as the system is prepared for more extensive outpatient use.

In conclusion, the ZMPC+HMS algorithms were shown to be feasible for use in the adolescent population. Also, the system was able to provide improved glycemic control compared to SAP, even in the ambulatory outpatient environment emulating real-life conditions. The controller was not informed of the twice-daily exercise sessions, but was able to react to the decreasing CGM measurements to attenuate, or suspend, insulin delivery during or after exercise, as needed. This study represents a promising step forward for the ZMPC+HMS AP system in the transition from inpatient

to outpatient evaluation, as well as in expanding the user population to include adolescents in addition to adults.

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