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Multivariable Artificial Pancreas for Various Exercise Types and Intensities

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Abstract

Background: Exercise challenges people with type 1 diabetes in controlling their glucose concentration (GC). A multivariable adaptive artificial pancreas (MAAP) may lessen the burden.

Methods: The MAAP operates without any user input and computes insulin based on continuous glucose monitor and physical activity signals. To analyze performance, 18 60-h closed-loop experiments with 96 exercise sessions with three different protocols were completed. Each day, the subjects completed one resistance and one treadmill exercise (moderate continuous training [MCT] or high-intensity interval training [HIIT]). The primary outcome is time spent in each glycemic range during the exercise + recovery period. Secondary measures include average GC and average change in GC during each exercise modality.

Results: The GC during exercise + recovery periods were within the euglycemic range (70–180 mg/dL) for 69.9% of the time and within a safe glycemic range for exercise (70–250 mg/dL) for 93.0% of the time. The exercise sessions are defined to begin 30 min before the start of exercise and end 2 h after start of exercise. The GC were within the severe hypoglycemia (<55 mg/dL), moderate hypoglycemia (55–70 mg/dL), moderate hyperglycemia (180–250 mg/dL), and severe hyperglycemia (>250 mg/dL) for 0.9%, 1.3%, 23.1%, and 4.8% of the time, respectively. The average GC decline during exercise differed with exercise type ($P=0.0097$) with a significant difference between the MCT and resistance ($P=0.0075$). To prevent large GC decreases leading to hypoglycemia, MAAP recommended carbohydrates in 59% of MCT, 50% of HIIT, and 39% of resistance sessions.

Conclusions: A consistent GC decline occurred in exercise and recovery periods, which differed with exercise type. The average GC at the start of exercise was above target (185.5 ± 56.6 mg/dL for MCT, 166.9 ± 61.9 mg/dL for resistance training, and 171.7 ± 41.4 mg/dL HIIT), making a small decrease desirable. Hypoglycemic events occurred in 14.6% of exercise sessions and represented only 2.22% of the exercise and recovery period.

Keywords: Exercise, Artificial pancreas, Type 1 diabetes.

Introduction

ARTIFICIAL PANCREAS (AP) systems monitor trends in blood glucose concentration (BGC) through a continuous glucose monitor (CGM) and use a control algorithm to calculate the appropriate insulin dose administered through

an insulin pump. This basic structure is proving to be a promising treatment approach that will simplify the lives of people with type 1 diabetes (T1D) as it can address many of the challenges they face. Compared with the baseline HbA1c values, preliminary hybrid-AP systems improve overall glycemic control with the average HbA1c of long-term

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outpatient AP use improved from 7.2% to 7.0% and from 7.4% to 6.9% for 6-month¹ and 3-month-long trials,² respectively. The American Diabetes Association recommends that adults with T1D achieve an HbA1c less than 7% to minimize the risk for diabetes-related complications and the early AP systems are helping people to achieve that strict glycemic control without increasing the risk of hypoglycemia.³ However, these hybrid systems still require a significant amount of user input such as entering meal information for insulin boluses and notifying the AP of physical activity (PA).

PA provides a challenge for people with T1D to maintain good control of their BGC and AP systems. Numerous factors influence the glucose response due to exercise such as the type, duration, intensity, insulin-on-board, and degree of stress involved. The intensity of the PA plays a large role in the body's fuel metabolism, which leads to different glucose responses. For example, it is common for the BGC to decline during aerobic exercise and for the BGC to increase during anaerobic exercise.⁴ In addition, exercise can have a large impact on BGC for several hours after cessation of the activity.⁵ The glucose requirements for maintaining euglycemia increase during the immediate recovery period from exercise and again increase in the period 7–11 h after exercise cessation.⁵

AP systems need to be capable of compensating for the various forms of PA safely both during exercise and in the recovery periods. In 2010, the first study of overnight closed-loop control following daytime exercise demonstrated the AP's ability to minimize overnight hypoglycemia.⁶ The first published study of standardized exercise during closed-loop control consisted of pregnant women completing sessions of brisk treadmill walking.⁷ Numerous trials have since incorporated light or moderate-intensity exercise^{8–24} and others included interval and resistance exercise^{21,22} into their protocols. Various approaches have been studied to maintain optimal glycemic control throughout closed-loop control. These include the use of glucagon,^{8,17,23,24} using heart rate to inform the AP of exercise,¹² and using additional variables to improve the glucose predictions.^{21,22}

We propose a multimodule multivariable adaptive AP (MAAP) system for patients with T1D to regulate glucose concentration (GC) under various exercise types and intensities without requiring any manual information to be

entered by the user. The proposed AP system was tested over 18 three-day clinical experiments with 2 exercise sessions per day. The technical details of the proposed AP system are presented elsewhere.^{21,22,25,26}

Research Design and Methods

Experimental setup and inclusion criteria

Overall, 10 subjects participated in the 18 clinical closed-loop experiments. Table 1 shows the characteristics of the participants of the closed-loop studies. The study population includes young adults with T1DM ages 18–45 years who wear an insulin infusion pump. Potential subjects were excluded for clinical conditions or use of treatments (e.g., medications) that may be independently associated with cardiovascular disease (CVD) or recent metabolic instability. The specific exclusions include overt CVD; uncontrolled hypertension; history of retinopathy, nephropathy, or peripheral vascular disease; active illicit drug use; pregnancy; history of abnormal thyroid function; and metabolic instability during the last 2 months (e.g., diabetic ketoacidosis, hypoglycemic seizures, and hospitalization for a diabetes-related condition).

Details of procedures

The subjects arrived at the Clinical Research Center (CRC) of the University of Chicago at 07:00 hr on the first day of the experiment. The study was explained, and informed consent was obtained. Subjects wore their personal insulin pump, a CGM (Medtronic Guardian Real-Time Continuous Glucose Monitors, Northridge, CA, or Dexcom G4 Platinum, San Diego, CA), and a BodyMedia SenseWear Pro3, Pittsburgh, PA armband reporting PA via energy expenditure (EE) and galvanic skin response (GSR). Interstitial glucose (via CGM) and PA information was sent to the AP every 5 min. The control algorithm was run on a computer. PA information was sent to the computer wirelessly, while the CGM information was transferred through a wired connection when Dexcom sensors were used. In the experiments using the Medtronic Guardian CGM sensor, the CGM readings were entered to the computer manually. All experiments were performed over 60 h. Each individual used his or her personal glucometer for self-monitoring of blood glucose (SMBG)

TABLE 1. DEMOGRAPHIC INFORMATION FOR SUBJECTS

ID	Age (year)	Duration of diabetes (months)	BMI (kg/m ²)	Total daily basal insulin (U)	Gender	Race/ethnicity
S1	21	136	23.68	61.3	Male	White/non-Hispanic
S2	23	70	18.89	38.7	Male	White/non-Hispanic
S3	26	194	26.28	26.4	Male	White/non-Hispanic
S4	19	195	23.55	24.6	Female	White/non-Hispanic
S5	24	206	23.39	21.3	Male	African American
S6	24	124	25.5	21.0	Male	White/non-Hispanic
S7	33	358	38.62	18.7	Female	White/non-Hispanic
S8	22	129	23.75	25.8	Male	White/non-Hispanic
S9	34	381	24.78	16.9	Male	White/non-Hispanic
S10	25	209	25.48	16.8	Female	White/non-Hispanic
Average	25.1	200.2	25.39	27.14	7 Male/3 Female	9 White/non-Hispanic 1 African American

levels for calibration of the CGM and for blood glucose (BG) testing during PA. Subjects calibrated the CGM at least twice each day according to the manufacturer's instructions.

For safety, subjects were asked to test for blood ketones if BG >250 mg/dL using a Nova Max plus meter.²⁷ An intravenous catheter was placed at the start of day 1. BG levels were obtained every 30 min for 60 h (except during exercise), using a YSI (Yellow Spring Instruments) 2300 STAT PLUS glucose analyzer. The YSI or SMBG measurements were collected only for safety purposes and were not used in any part of the algorithm for insulin dosing. The assay is conducted in duplicate and controls are performed daily.²⁸

Prior to admission to the study, subjects were contacted by the research dietitian to plan the diet during their inpatient stay according to their habitual intake. Individual energy needs were determined using the Mifflin-St. Jeor equation.²⁹ Diet planning and analysis were completed using Food Processor SQL from ESHA Research (Elizabeth Stewart Hands and Associates, Salem, OR). All meals were prepared under supervision by a registered dietitian nutritionist in the University of Chicago CRC Metabolic Kitchen.

The study diet consisted of a one-day menu of three meals and one evening snack. Identical meals were provided each day of the study. Breakfast provided 25% of calories, lunch 30%, dinner 35% and evening snack 10%. The macronutrient composition of the diet was 40–50% of calories from carbohydrate, 20–30% from protein, and 30–35% from fat. Subjects were not required to consume 100% of weighed research meals provided and anything not consumed was weighed back. Subjects were not allowed to consume any foods or beverages not provided by the metabolic research kitchen. Breakfast, lunch, dinner meals and evening snacks occurred at the same time each day. Subjects were also provided with a variety of snacks based on individual food preferences to be used on an as needed basis (for prevention of hypoglycemia as indicated by the AP algorithm).^{14,25,26}

At the conclusion of the study, the subject's insulin pump and CGM were downloaded, and then, individual settings were resumed. One to 2 h later, the subject was discharged from the CRC and contact was made with the study team when the subject returned home.

Exercise protocol

Subjects completed two bouts of exercise per day, for three consecutive days, as shown in Figure 1. Each bout of exercise was scheduled 6 h apart. Days 1 and 3 consisted of aerobic, moderate continuous training (MCT), and resistance training (RT). MCT was prescribed with the heart rate reserve method

($HHR = [HR_{max} - HR_{rest}] \times \% \text{ intensity desired} + HR_{rest}$) with HR_{max} measured during a maximal exercise stress test (Bruce protocol) and HR_{rest} measured after 15 min of sitting before this experiment. The MCT consisted of a warm-up period of 5 min, then 20 min of 60%–80% heart rate reserve (HRR), and finally a 5-min cool down. RT was guided by rating of perceived exertion of 11–15 (6–20-point Borg Scale), with subjects performing 3 sets of 10 repetitions on 4 exercises (leg extension, seated chest press, seated row, and lat pull-down). On Day 2, subjects first completed RT, and then high-intensity interval training (HIIT) (6 h post RT). HIIT training included a 5-min warm-up, followed by 3 min of treadmill exercise at 60%–70% HHR followed by 4 min at 80%–90% HRR; this was then repeated three times, such that four bouts of high intensity and three bouts of lower intensity were completed for a total of 36 min.

A guide was given to subjects to help visualize protocol as shown in Supplementary Figure S1 (Supplementary Data are available at <http://online.liebertpub.com/suppl/doi/10.1089/dia.2018.0072>).³⁰ The exercise sessions are defined to begin 30 min before the start of exercise and end 2 h after start of exercise. The reason we did not define the exercise session to be from the start of exercise is because the participants had to walk from the CRC to the physical therapy laboratory located in a different part of the building where the exercise was completed.

Closed-loop system

The MAAP system is based on a generalized predictive control (GPC) algorithm. In MAAP, the BGC is modeled by an autoregressive moving average model with exogenous inputs (ARMAX) with inputs GSR, EE, and the subcutaneous glucose value from the CGM. After the unknown model parameters are estimated, the appropriate amount of insulin to be infused is calculated by a constrained minimization problem.^{21,22} In the early experiments (S1-E1; S2-E1; S4-E1, E2; S5; S6-E1, E2; S7; S9; S10-E1), the appropriate insulin was given as a basal rate (U/H) and in the later experiments (S1-E2, E3, E4; S2-E2; S3-E1, E2; S8; S10-E2), the subject's predefined standard basal rate and the GPC calculated insulin boluses (U) were used. In the experiments in which the subject's basal rate was utilized as a baseline, the controller alternated periods of pump suspension when the rate was too high and added small boluses when the rate was too low; thus, the basal rate was still adjusted by the controller based on the calculated needs of the individual.

Specialized modules enhance the MAAP performance such as a hypoglycemia early alarm system,^{22,31} a meal detection algorithm,³² and a hypoglycemia prediction and

FIG. 1. The exercise type and frequency protocol.

carbohydrate recommendation algorithm.³³ All presented clinical data utilized the hypoglycemia early alarm algorithm in which CGM, insulin-on-board, and PA signals are used to predict hypoglycemia 25 min in advance.^{3F} This algorithm was updated to suggest an appropriate amount of carbohydrates based on the current BGC and its rate of change to prevent the potential hypoglycemia episode³³ in the following experiments (S1-E1, E2, E3, E4; S2-E1, E2; S3-E1, E2; S4-E2; S5; S7; S8; S10-E2). The meal detection algorithm administered meal boluses based on CGM measurements, a modified Bergman's minimal model, and an unscented Kalman filter for state estimates and this algorithm was used in all but three of the presented experiments (S1-E1, E2, E3, E4; S2-E1, E2; S3-E1, E2; S4-E2; S5; S6-E2; S7; S8; S9; S10-E2). The modules used in each experiment are shown in Supplementary Figure S2.

Statistical methods

The primary outcome measure of interest in this study is the time spent in each glycemic range (severe hypoglycemia [<55 mg/dL], moderate hypoglycemia [55 – 70 mg/dL], euglycemia [70 – 180 mg/dL], and moderate hyperglycemia [180 – 250 mg/dL], severe hyperglycemia [>250 mg/dL], and safe glycemic range [70 – 250 mg/dL]) during the combined exercise and recovery period (30 min before exercise onset through 2 h after exercise onset) based on the CGM values. The secondary measures of interest include the average GCs and the average change in GCs during each exercise modality. The secondary outcome measures are considered for both the combined exercise and recovery period (two-and-a-half hour period) and when considering the exercise and recovery periods separately (the exercise period consisting of the time spent completing the exercise protocol and recovery period beginning at the end of exercise through 90 min after the end of exercise).

To compare these outcome measures between the three exercise modes, single-factor analysis of variance (ANOVA) and Tukey's honest significant difference tests were used. In all cases, a significance level of 5% was considered. To mitigate the effect of some participants completing multiple trials of the experiment and others completing just one experiment on our statistical analysis, bootstrap ANOVA was applied. Each bootstrap sample was drawn from the original data set at random with replacement. One thousand bootstrap samples were drawn, and the one-way ANOVA was applied to each.³⁴ The mean absolute relative difference (MARD) was calculated to compare CGM performance.³⁵

Results

In three experiments (S4-E1, S9-E1, and S10-E1), a Medtronic Guardian CGM was used, and in the other 15 experiments, a Dexcom G4 CGM was used. There are a few exceptions to the above exercise protocol: S3-E1, S3-E2, S4-E1, S5-E1, and S7-E1 did not complete the MCT sessions on day 1; S1-E1, S4-E1, and S9-E1 did not complete the MCT session on day 3; S5-E1 did not complete the RT exercise session on the first day; and S1-E1 did not complete the RT session on the second day.

Table 2 shows the average clinical outcomes of the MCT exercise sessions and subject-specific outcomes can be found in S-Table 1. Overall 74.12% of the time glucose values are observed within the desired target range. In all MCT sessions, a consistent decrease in glucose levels was observed with an average change in glucose values of (-99 ± 60.4 mg/dl) compared to starting glucose levels (185.5 ± 56.6 mg/dl). Figure 2 (top) shows the mean and standard deviation of the CGM traces during the MCT sessions over all the subjects where the mean glucose levels are within the desired target range during the combined exercise and recovery period.

Based on the CGM readings, severe hypoglycemia was observed only during two of the MCT sessions (S1-E1 and S10-E2 in S-Table 1). In S1-E1, the subject began the experiment in hyperglycemia (298 mg/dL) and the algorithm recommended 4.8 units of insulin 10 minutes into the experiment. The first MCT session began 30 minutes into experiment which led to a severe decline in BGC. At the beginning of exercise, the CGM reading was 243 mg/dl and the fingerstick was 164 mg/dl while at end of exercise, CGM was 112 mg/dl and fingerstick was 38 mg/dl. This fingerstick was confirmed with a repeated test. This indicates that the inaccuracy of the CGM sensor (MARD: 48.34%) played a big role in causing the severe hypoglycemia possibly because of its inability to track rapid changes in BGC and the gap in glucose concentration readings because of the 5-minute sampling time. The severe hypoglycemia that was observed in the CGM during S10-E2 was the result of inaccurate measurements, as the YSI (or fingerstick) measurements were greater at that time. The lowest confirmatory YSI reading during this session was recorded to be 63 mg/dl.

Table 2 shows the average clinical outcomes of the RT exercise sessions, and subject-specific outcomes are found in Supplementary Table S2. In RT exercise sessions, 67.8% of CGM values fell within the target range of 70–180 mg/dL and 91.0% of CGM values fell within the range of 70–250 mg/dL. Severe hypoglycemia is observed in only one session, S5-E1, with a YSI confirming the BGC to be 55 mg/dL, but the CGM

TABLE 2. PERFORMANCE INDEXES BASED ON CONTINUOUS GLUCOSE MONITOR DATA FOR EACH EXERCISE (30 MIN BEFORE THE START OF EXERCISE THROUGH 2 H AFTER), ALL EXERCISES (30 MIN BEFORE THE START OF EXERCISE THROUGH 2 H AFTER), AND THE WHOLE EXPERIMENT (~60 H)

Time of interest	55> (%)	55–70 (%)	70–180 (%)	180–250 (%)	250< (%)	Mean $\pm$ SD (mg/dL)
MCT exercise	1.73 $\pm$ 5.03	1.29 $\pm$ 2.58	74.12 $\pm$ 16.51	17.32 $\pm$ 12.30	5.55 $\pm$ 10.48	142.27 $\pm$ 46.41
RT exercise	1.03 $\pm$ 4.37	1.68 $\pm$ 2.98	67.82 $\pm$ 17.75	23.18 $\pm$ 15.62	6.29 $\pm$ 10.38	152.30 $\pm$ 51.32
HIIT exercise	0.00 $\pm$ 0.00	1.64 $\pm$ 4.27	68.87 $\pm$ 20.29	29.14 $\pm$ 20.80	0.35 $\pm$ 1.45	150.48 $\pm$ 31.09
All exercises	0.88 $\pm$ 2.15	1.34 $\pm$ 1.55	69.92 $\pm$ 12.79	23.07 $\pm$ 10.88	4.79 $\pm$ 6.55	150.71 $\pm$ 49.72
Whole experiment	0.55 $\pm$ 0.74	1.97 $\pm$ 1.37	76.75 $\pm$ 12.04	17.24 $\pm$ 8.96	3.49 $\pm$ 4.05	143.33 $\pm$ 45.63

HIIT, high-intensity interval training; MCT, moderate continuous training; SD, standard deviation; RT, resistance training.

FIG. 2. Glucose traces (mean and standard deviation) during MCT, RT, and HIIT exercises. The solid black line represents the mean of CGM, and the shaded gray region represents one standard deviation of CGM for all experiments. Dotted lines indicate hypoglycemia (70 mg/dL) and hyperglycemia (180 mg/dL). CGM, continuous glucose monitor; HIIT, high-intensity interval training; MCT, moderate continuous training; RT, resistance training.

continued to indicate a severe hypoglycemia value for 20 min after a fingerstick of 68 mg/dL, which is a high percentage of the 2.5-h time window. While severe hypoglycemia did occur, the percent of time in each range may be unreliable in S5-E1 as the CGM performance was poor (MARD = 35.72).

In the RT exercise sessions, a consistent decrease in the CGM values was observed with an average change in glucose values (-65.7 ± 72.6 mg/dL) compared with the average starting glucose value (166.9 ± 61.9 mg/dL). The decline in glucose values is to be expected as the exercise was primarily aerobic with the subject's heart rate getting in the anaerobic range (HRR >80%) only an average of 1.75% of the time. Figure 2 (middle) shows the mean and standard deviation of the CGM traces during the RT exercise sessions over all the experimental sessions and, as shown, the mean glucose levels are well within the desired target range for the duration of the exercise and recovery periods. While the percentage of time spent in hypoglycemia is high in some experiments, it is important to consider that some percent of the total 2.5-h time window for pre-exercise, exercise, and recovery considered in this analysis is a relatively short period of time.

Table 2 shows the average clinical outcomes of the HIIT exercise sessions and subject-specific outcomes are found in Supplementary Table S3. In HIIT exercise sessions, the CGM values were within the target range of 70–180 mg/dL for 68.9% of the time and the values were maintained in the safe range of 70–250 mg/dL for 98.0% of the time. There were no episodes of severe hypoglycemia during the combined exercise and recovery period for the HIIT sessions. A consistent decline in the glucose values was observed with an average change in glucose values during the exercise and recovery periods of -78.2 ± 47.9 mg/dL from the initial CGM values (171.7 ± 41.4 mg/dL), yet the average glucose value for the exercise and recovery periods was 150.5 ± 31.1 mg/dL. Figure 2 (bottom) shows the mean and standard deviation of the CGM traces during the HIIT exercise sessions over all the experimental sessions, and again, the mean glucose levels are

well within the desired target range for the duration of exercise and recovery periods.

The clinical outcomes of the combined exercise data are presented in Table 3. The glucose values were within the euglycemic range (70–180 mg/dL) for 69.9% of the time and were within the safe range for exercise of 70–250 mg/dL for 93.0% of the time. Three subjects experienced severe hypoglycemia as indicated by CGM within the exercise sessions; however, only two of those cases were confirmed with YSI or fingerstick values in the severe range and in the third case, the repeated fingerstick measurements indicated only mild hypoglycemia. These hypoglycemic episodes were described at greater length in the respective exercise modality summaries. The number of hypoglycemic episodes during all exercise sessions was 14.6%: in 5 of the 27 MCT sessions, 3 of the 18 HIIT sessions, and 6 of the 51 RT sessions. The AP recommended carbohydrates to prevent or minimize these episodes of hypoglycemia in 16 of the MCT sessions, 9 of the HIIT sessions, and 20 of the RT sessions, corresponding to 59%, 50%, and 39% of the sessions of each exercise type, respectively.

The average CGM value during the combined exercise and recovery periods was slightly higher in RT and HIIT exercise than in the MCT exercise sessions with values of 152.3, 150.5, and 142.3 mg/dL, respectively, but there was no statistically significant difference between them ($P=0.578$). Considering the period of 30 min before exercise onset through 2 h after exercise onset, the average decline in glucose during the three types of exercise differed with exercise type ($P=0.0017$). Further analysis showed that there was a statistically significant difference in the change in CGM values between the MCT and HIIT sessions ($P=0.0011$), but there was no statistically significant difference between the MCT and RT sessions ($P=0.139$) or the RT and HIIT sessions ($P=0.0753$). It is unlikely that this change was affected by the CGM value at the start of exercise as there was again no statistically significant difference between the three groups ($P=0.437$).

TABLE 3. PERFORMANCE INDEXES BASED ON CONTINUOUS GLUCOSE MONITOR DATA FOR ALL EXERCISES (30 MIN BEFORE THE START OF EXERCISE THROUGH 2 H AFTER)

Subject	Experiment	55> (%)	55–70 (%)	70–180 (%)	180–250 (%)	250< (%)	Mean $\pm$ SD (mg/dL)
S1	E1	2.84	1.17	54.01	31.61	10.37	167.00 $\pm$ 57.51
	E2	0.00	3.97	74.97	20.66	0.40	140.71 $\pm$ 47.94
	E3	0.00	2.78	74.17	20.66	2.38	149.36 $\pm$ 45.20
	E4	0.00	0.79	79.60	16.56	3.05	134.79 $\pm$ 45.07
S2	E1	0.00	0.00	66.49	25.70	7.81	158.33 $\pm$ 52.38
	E2	0.00	0.00	77.48	22.52	0.00	142.01 $\pm$ 45.06
S3	E1	0.00	0.00	68.05	31.95	0.00	147.23 $\pm$ 45.38
	E2	0.00	2.65	90.07	7.28	0.00	124.24 $\pm$ 35.19
S4	E1	0.00	0.00	43.29	37.43	19.28	198.80 $\pm$ 55.79
	E2	0.00	4.50	55.76	24.77	14.97	167.28 $\pm$ 79.77
S5	E1	6.18	3.09	66.00	6.62	18.10	155.78 $\pm$ 84.48
S6	E1	0.00	1.10	67.00	31.13	0.77	146.66 $\pm$ 49.34
	E2	0.00	1.11	90.42	8.46	0.00	153.29 $\pm$ 41.55
S7	E1	0.00	0.00	68.54	31.46	0.00	143.62 $\pm$ 47.14
S8	E1	0.00	0.00	69.80	27.81	2.38	157.57 $\pm$ 37.09
S9	E1	0.00	0.00	74.01	24.50	1.49	141.68 $\pm$ 57.69
S10	E1	0.00	0.00	53.09	41.76	5.15	176.74 $\pm$ 42.85
	E2	6.85	2.88	85.87	4.38	0	102.86 $\pm$ 33.49
	Average	0.88	1.34	69.92	23.07	4.79	150.71 $\pm$ 49.72

In analyzing the exercise and recovery periods separately (exercise period consisting of start of exercise through end of exercise and recovery period consisting of end of exercise through 90 min after end of exercise), the results differ from the comparison of the two time windows together. Again, there is not a statistically significant difference in the mean CGM values during exercise or recovery ($P=0.4470$ and $P=0.1898$, respectively). However, the change in CGM during the exercise periods was significant ($P=0.0097$) with a significant difference between the MCT and RT ($P=0.0075$), but no significant difference between the MCT and HIIT ($P=0.5210$) or RT and HIIT ($P=0.3255$). In the 90-min recovery periods, there was no significant difference in the change in CGM between the three exercise modalities ($P=0.1668$). In a few cases, the subjects opted to have a snack in the 2-h period following exercise. If the effect of these subject-selected carbohydrates was neglected by shortening the recovery period to 30 min, statistical significance was again not achieved in the mean glucose values ($P=0.0556$) or in the change in glucose values ($P=0.0900$).

The MAAP maintained the glucose values inside the target euglycemic range (70–180 mg/dL) for 76.8% of the experiments and within the safe range of 70–250 mg/dL for 94% of the time (Table 2). In comparison with the exercise periods, the time spent in the euglycemic range increased by 6.9%, while the time spent in the range of 70–250 mg/dL only increases by 1%. The time spent in hypoglycemia is low when considering the total period of the experiments, with only an average of 0.55% and 1.97% for severe and mild hypoglycemia, respectively. Supplementary Table S4 presents the clinical outcomes of the entire duration of each experiment. The total insulin doses administered by the MAAP system are outlined in Supplementary Table S5 with the values representing the total dose per day.

To study the influence of the unequal number of experiment sessions completed by each participant on our statistical analysis, the outcomes of the one-way ANOVA are compared with one-way ANOVA calculated on bootstrap samples. The

results are presented in Supplementary Table S6. Statistical significance was achieved in the same cases with one exception. In considering the change in glucose values during the exercise period, ANOVA conducted on the original samples resulted in $P=0.0097$, but when the ANOVA was conducted on each of the bootstrap sample sets, $P=0.0525 \pm 0.124$ (mean $\pm$ standard deviation).

Figure 3 and Supplementary Figures S3–S19 outline the details and specific timing of interventions of each experimental session. Figure 3 represents S1–E4 and in this experiment, the algorithm successfully maintains euglycemia during the exercise sessions and recovery period 96.16% of time in 70–250 mg/dL (134.79 ± 45.07 mg/dL). The subject completed two continuous, moderate-intensity aerobic exercise sessions 100.0% of time in 70–250 mg/dL (123.99 ± 32.16 mg/dL), one session of intermittent high-intensity exercise 98.01% of time in 70–250 mg/dL (147.01 ± 36.90 mg/dL), and three sessions of resistance exercise 84.67% of time in 70–250 mg/dL (131.93 ± 69.72 mg/dL). The algorithm recommended carbohydrates to prevent hypoglycemia during exercise and recovery, which included carbohydrate consumption at 10:49, 17:00, and 17:29 hr on the first day, 10:36 and 14:47 hr on the second day, and 8:54, 9:11, 9:29, and 15:25 hr on the third day. The high insulin-on-board during the fourth and fifth exercise sessions led to a significant decline in BG during the exercise period; yet, the algorithm was capable of preventing severe hypoglycemia throughout the entire experiment.

The overall performance in this experiment was satisfactory with 81.20% of time spent in 70–180 mg/dL and 96.80% of time in 70–250 mg/dL, while CGM error was present with an MARD of 13.28. Breakfast consisted of 67 g of carbohydrates, the midmorning snack 30 g, lunch 82 g, the afternoon snack 30 g, dinner 91 g, and the evening snack 26 g. The total daily calorie consumption due to scheduled meals was 2785 kCal. All rescue carbohydrates were recommended by the early alarm system, and the doctor did not need to recommend any additional carbohydrate consumption. The subject consumed rescue carbohydrates on the first day at 14:44 hr, on the second

FIG. 3. Visual representation of MAAAP performance in one experiment. MAAAP, multivariable adaptive artificial pancreas.

day at 00:11, 2:50, and 3:05 hr, and on the third day at 00:06, 3:51, 3:56, 5:26, 6:55, 13:35, 14:05, and 14:25 hr.

Discussion

The MAAP system is demonstrated in the 96 exercise sessions of three different exercise protocols, and the time spent in hypoglycemia is low despite the lack of any user announcements for exercise. In an open-loop setting, it is expected that the MCT exercise would lead to a decrease in BGC; the HIIT exercise may decrease, increase, or lead to a stable BGC; and the RT exercise may lead to an increase in BGC if conducted at a high intensity or a decrease if conducted at a low to moderate intensity. In a system that does not require the user to input exercise information, it is expected that exercise will lead to similar BGC responses; however, the MAAP mitigates the change in BGC enough to prevent dangerous glycemic excursions most of the time.

Under MAAP control, across the three exercise modalities, a consistent decline in BGC was observed in the combined exercise and recovery period. The observed BGC changes differed between exercise protocols. In considering the exercise periods alone, there was a statistically significant difference in the change in CGM between the MCT and RT. Yet, despite there being no statistically significant difference in the change in CGM values during the recovery period, when the combined exercise and recovery period is considered together, there was an observed statistically significant difference between the MCT and HIIT exercise sessions.

The MAAP was able to maintain safety and minimize the prevalence of hypoglycemia independent of exercise type. The number of hypoglycemic events observed in the unannounced exercise sessions is occurring in 14.6% of sessions, despite requiring the system to detect the onset of exercise and predict a decline in glucose before measures to prevent hypoglycemia could be taken. In addition, a number of these events could have been prevented as subjects were advised by the hypoglycemia early alarm and carbohydrate recommendation algorithm to consume carbohydrates; however, some subjects decided not to follow these recommendations until the next meal or when the glucose began to decline rapidly. As exercise occurred ~2 h after the subjects consumed a meal (in a system without meal announcements), the insulin-on-board at exercise onset was generally high, which amplifies the challenge of maintaining euglycemia. Despite these hurdles, the MAAP can maintain similar and acceptable average glucose levels during moderate-intensity aerobic, high-intensity interval, and resistance exercise.

There is a valid concern that hypoglycemia cannot be evaded if the presence of PA is detected at the beginning of an exercise and even if insulin infusion is stopped at that instant. MAAP attempted to prevent many potential hypoglycemic episodes by aggressively reducing insulin infusion rate and by issuing a hypoglycemia alert and recommendations to consume rescue carbohydrates well in advance of a potential hypoglycemic event. These insulin adjustments and carbohydrate recommendations occurred even if the subject was in the hyperglycemia range and the algorithm determined rapid insulin decline and presence of exercise.

The outcomes of this study are comparable with other recent AP trials which include exercise. This study has challenged

our AP through unannounced meals and unannounced exercise of multiple protocols, both of which can hinder performance, so it is not feasible to compare this study with other AP systems that utilized different protocols. An important difference of MAAP from other APs that use exercise information for control decisions is the inclusion of the physiological variables in the dynamic model that predicts future GCs. This enables more accurate predictions especially during exercise and recovery periods. In a recent study, an AP system outperformed sensor-augmented pump therapy in terms of increased time in the euglycemic range and a reduction in the exposure to hypoglycemia in adolescents at a skiing and snowboarding camp.³⁶ Another study has shown improvements in performance due to inclusion of heart rate to influence the insulin dosing, which outperformed the standard AP system without heart rate in terms of reducing hypoglycemia.³⁷

The average glucose level during the experiments is 143.33 mg/dL, which if maintained over time would correspond to an HbA_{1C} of 6.6%, and the average glucose level during exercise was 150.71 mg/dL, which corresponds to an HbA_{1C} of 6.9%,³⁸ both of which achieve the target HbA_{1C} for young adults set by the American Diabetes Association.³

As is expected, the MAAP performance is highly dependent on the accuracy of the CGM. The percentage of time spent in the euglycemic range (70–180 mg/dL) was inversely proportional to the MARD of the CGM with the lower error rate corresponding to improved performance. This relationship was highly statistically significant during the exercise and recovery periods ($P=0.0035$). This general trend is observed when considering the entire experiment duration, but two outliers prevent statistical significance. As the CGM technology continues to improve, we anticipate this will be less of a hindrance for MAAP performance in the future.

The MARD values for the CGMs used in this experiment may have been increased due to two limitations of the study: the participants used their personal glucometers, and the CGM calibration may have occurred in nonideal glucose trends. CGM accuracy is greatest when the CGM is calibrated during a stable glucose period (flat arrows on CGM), but this was not always the case when the subjects chose to calibrate. There were high MARD experiments for both Medtronic and Dexcom sensors and these errors may be partially attributed to these limitations.

Despite all the promising results, the present study has some limitations:

- There was no control arm so the performance of the MAAP system cannot be compared with any standard of care (e.g., MDI). Multiple modifications were made to the algorithm over the course of the study and some subjects used various versions of the algorithms.
- The total number of MCT, RT, and HIIT exercise sessions was not balanced, and potentially may have impacted on the statistical results.
- The order of the exercise sessions was not randomized, which may also have impact on the statistical results.
- Although the experiments are designed to be close to normal-life conditions as much as possible, the proposed algorithm should be tested under real-life conditions in home or hotel settings.

Conclusions

As many individuals with T1D fail to achieve their glycemic targets, the MAAP system could lessen their burden and help them to achieve those goals without requiring them to make meal or PA announcements. The efficacious performance of MAAP is demonstrated in 96 exercise sessions of 3 different protocols. As is consistent with literature, the largest decline in BGC was observed during the moderate-intensity exercises (MCT and HIIT) compared with the resistance exercise, with a statistically significant difference between the MCT and RT exercise. Similarly, the MAAP hypoglycemia early alarm and carbohydrate recommendation algorithms had the greatest number of alarms in the MCT, followed by HIIT and last the RT. This further indicates that the MAAP system was able to manage glucose during the three exercise protocols, while the glycemic excursions were consistent with the expected trends based on the intensity of the exercise sessions.

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Author Disclosure Statement

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