# Randomized Outpatient Trial of Single- and Dual-Hormone Closed-Loop Systems That Adapt to Exercise Using Wearable Sensors

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## OBJECTIVE

**Automated insulin delivery is the new standard for type 1 diabetes, but exercise-related hypoglycemia remains a challenge. Our aim was to determine whether a dual-hormone closed-loop system using wearable sensors to detect exercise and adjust dosing to reduce exercise-related hypoglycemia would outperform other forms of closed-loop and open-loop therapy.**

## RESEARCH DESIGN AND METHODS

**Participants underwent four arms in randomized order: dual-hormone, single-hormone, predictive low glucose suspend, and continuation of current care over 4 outpatient days. Each arm included three moderate-intensity aerobic exercise sessions. The two primary outcomes were percentage of time in hypoglycemia (<70 mg/dL) and in a target range (70–180 mg/dL) assessed across the entire study and from the start of the in-clinic exercise until the next meal.**

## RESULTS

**The analysis included 20 adults with type 1 diabetes who completed all arms. The mean time (SD) in hypoglycemia was the lowest with dual-hormone during the exercise period: 3.4% (4.5) vs. 8.3% (12.6) single-hormone ($P = 0.009$) vs. 7.6% (8.0) predictive low glucose suspend ($P < 0.001$) vs. 4.3% (6.8) current care where pre-exercise insulin adjustments were allowed ($P = 0.49$). Time in hypoglycemia was also the lowest with dual-hormone during the entire 4-day study: 1.3% (1.0) vs. 2.8% (1.7) single-hormone ($P < 0.001$) vs. 2.0% (1.5) predictive low glucose suspend ($P = 0.04$) vs. 3.1% (3.2) current care ($P = 0.007$). Time in range during the entire study was the highest with single-hormone: 74.3% (8.0) vs. 72.0% (10.8) dual-hormone ($P = 0.44$).**

## CONCLUSIONS

**The addition of glucagon delivery to a closed-loop system with automated exercise detection reduces hypoglycemia in physically active adults with type 1 diabetes.**


Automated insulin delivery is emerging as the new standard for managing type 1 diabetes. There are multiple advantages to insulin automation over standard sensor-augmented pump therapy (1). The most evident advantage is the system's responsiveness to changes in insulin sensitivity. Automated insulin delivery has the potential to significantly reduce dysglycemia but does not replicate normal glucose homeostasis. The delayed onset and

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prolonged action of insulin administered subcutaneously can lead to postprandial hyperglycemia and hypoglycemia late after meals (2). Exercise is also a major challenge. The consumption of glucose by working muscles and the increase in insulin sensitivity lasting 8–24 h after exercise significantly increases the risk for hypoglycemia (3). Multiple research groups (4–8) have proposed to mitigate the risk of hypoglycemia in patients with type 1 diabetes with the use of glucagon as a part of a dual-hormone closed-loop system. Glucagon is normally secreted by the $\alpha$-cell and functions primarily by glycogenolysis (9). Our prior work has shown that a dual-hormone system can reduce hypoglycemia when exercise is announced at the start of exercise compared with no announcement during an inpatient study (5). Here we extend our prior work by *1*) incorporating automated exercise and dosing adjustment into a 4-day outpatient setting and *2*) comparing a dual-hormone system with a single-hormone system, both of which automatically adapt to exercise using an algorithm (10) designed to prevent hypoglycemia.

## RESEARCH DESIGN AND METHODS

### Participants and Study Design

From August 2016 to June 2017, 25 adults with type 1 diabetes were enrolled at Oregon Health & Science University (OHSU). All participants provided written informed consent before participating in the study, which was conducted under a U.S. Food and Drug Administration–approved investigational device exemption and OHSU Institutional Review Board approval.

The inclusion criteria were a diagnosis of type 1 diabetes for at least 1 year, age 21–45 years, use of an insulin pump, ability to perform 45 min of exercise, and participants were required to be living with another adult. The exclusion criteria included a history of cardiovascular, kidney, or liver disease, or uncontrolled hypertension. Other exclusion criteria included pregnancy, severe hypoglycemia in the past 12 months, hypoglycemia unawareness, oral or parenteral corticosteroid use, seizure disorder, immunosuppressant use, or contraindication to glucagon delivery. Of the 25 that passed screening, 20 participants completed all four studies and were included in the data analysis, as shown in Supplementary Fig. 1. See Table 1 for their baseline characteristics. Four participants withdrew from the study due to scheduling conflicts. The investigator withdrew one patient after the patient had nausea/vomiting during the predictive low glucose suspend arm and was diagnosed with gastroparesis.

**Table 1—Baseline characteristics**

| Characteristic | Values |
|---|---|
| Age (years) | 34.5 (4.7) |
| Weight (kg) | 77.4 (16.0) |
| Sex | |
| Male | 9 |
| Female | 16 |
| $HbA_{1c}$ (%) | 7.5 (0.9) |
| $HbA_{1c}$ (mmol/mol) | 58 (9.8) |
| Diabetes duration (years) | 20.2 (8.9) |
| CGM users | 13 |

Data are mean (SD) or *n*.

### Randomization

Subjects were randomized to the four arms of the study using a Latin squares design in blocks of four.

### Procedures

After a 2-week run-in period to optimize pump settings and train participants on the t:slim pumps (Tandem, San Diego, CA) and Dexcom continuous glucose monitor (CGM), participants underwent four study arms, each lasting 4 days. In randomized order, participants used one of the following systems: *1*) dual-hormone closed-loop system, *2*) single-hormone closed-loop system, *3*) predictive low glucose suspend system, and *4*) continuation of current management (current care). Participants in all four study arms wore a G5 (Dexcom, San Diego, CA). Sensors were placed 24–72 h before the intervention visits and were calibrated every 12 h. The CGM data were transmitted to the study phone and blinded to the patient only during current care, although participants were allowed to use their own CGM during current care. On days 1 and 4 of each arm, participants remained in the clinic for 12 h and ate a self-selected breakfast, lunch, and dinner on day 1. The same meals were provided on day 4. After breakfast, participants completed activities of daily living such as washing dishes and sweeping the floor. Participants ate lunch at ~12 P.M. At 2 P.M., participants performed aerobic exercise on a treadmill for 45 min at 60% of their $VO_{2max}$. The heart rate required to reach 60% of their $VO_{2max}$ was determined during the $VO_{2max}$ test. For all study sessions, participants were treated with 15 g carbohydrate if capillary blood glucose (CBG) was <70 mg/dL. Study arms were spaced by 7–45 days.

### System Description

The closed-loop algorithm is a modified fading memory proportional-derivative algorithm (11). The control algorithm was run on a Nexus phone (Google, Mountain View, CA), which communicated via Bluetooth Low Energy (BTLE) to the t:slim pump(s) to adjust the delivery rate(s) every 5 min based on the Dexcom G5 reading (see Supplementary Fig. 2). The insulin pumps were filled with aspart insulin (Novo Nordisk, Plainsboro, NJ), and for the dual-hormone system, GlucaGen (Novo Nordisk) was reconstituted every 24 h. With the exception of the current care arm, participants were remotely monitored. Alarms were sent to study staff if the CGM reading was <40 mg/dL or >400 mg/dL or if the patient did not respond to system alarms.

Both of the closed-loop algorithms incorporated a previously described exercise detection algorithm that used inputs from a heart rate monitor and accelerometer, the ZephyrLife BioPatch (10). The detection algorithm used a regression equation to estimate metabolic equivalent to task (MET). Exercise detection occurred when METs exceeded 4 for ≥5 sequential minutes. Once exercise was detected, the participant was prompted to confirm that he or she was exercising. As previously described (10), after exercise detection and user confirmation, insulin was turned off for 30 min and then reduced by 50% of the typical rate called for by the control algorithm for 60 min. For the dual-hormone system, in addition to the insulin adjustments, the target glucose for glucagon was increased from 95 mg/dL to 120 mg/dL, and the maximum dose of glucagon allowed was increased by a factor of 2. The dual-hormone algorithm was also adaptive. On day 1, if the patient developed hypoglycemia within the first 1.5 h after exercise, the glucose target for glucagon was increased from 120 mg/dL to 130 mg/dL, resulting in glucagon being delivered sooner after exercise detection. The predictive low glucose suspend system used a Dexcom G5 and a t:slim pump programmed with the patient's basal rates, correction factors, and carbohydrate ratios. The predictive suspension algorithm was designed to replicate the Medtronic 640G (12). The predictive low glucose suspend system suspended insulin delivery when glucose was 70–140 mg/dL

and predicted to drop <90 mg/dL within 30 min. Insulin delivery resumed when glucose was 70–140 mg/dL and predicted to be >120 mg/dL within 30 min. Prediction of sensor glucose was based on linear regression of the prior 10 min.

### Outcomes

The prespecified primary outcomes were percentage time in hypoglycemia (CGM < 70 mg/dL) and time in range (CGM 70–180 mg/dL) assessed from the start of the in-clinic exercise until the next meal and across the entire study. Percentage of time was used rather than absolute time to adjust for differences in study length, which occurred such as when a patient arrived late. Secondary outcome measures were mean sensed glucose, number of carbohydrate treatments, percentage of time with CGM >180 mg/dL, number of CBG events <50 mg/dL and <70 mg/dL, and total amount of insulin and glucagon delivered. Time with CGM <54 mg/dL and >250 mg/dL were added post hoc to be consistent with a 2017 consensus report on outcomes (13). The primary outcomes were also evaluated post hoc during a nighttime period defined as midnight to 6 A.M. (13,14).

### Statistical Analysis

From a previous study, we estimated that 20 participants would yield >80% power to detect a paired difference of −3.3% time in hypoglycemia (SD 4) or +16.3% time in euglycemia (SD 20), which we approximated with a one-sample *t* test and a reduced $\alpha$ of 0.0125 (0.05/4) to allow for later pairwise comparisons of the arms.

In the analysis, we modeled the mean differences between study arms using linear mixed effects regression (or negative binomial for count outcomes) with a random intercept, controlling for possible carryover or learning effects. To compensate for some skew and heteroscedasticity, we used robust (Huber/White/sandwich) variance estimators and compared these against bootstrapped (nonparametric) SEs, which are not presented here but are available from us, and were similar for all outcomes. We checked whether conclusions would differ when omitting extreme values or under multiple imputation of missing values. Because we present a large number of end points comparing four conditions, we provide the Benjamini-Hochberg method to control the false discovery rate at 0.05 across all comparisons performed, because this method allows for correlation between outcomes (15,16). The sensitivity and specificity of the exercise detection algorithm were evaluated as follows: A true positive was defined as detection at least 30 min before the actual start of the exercise or no later than 10 min after the true start of exercise. This definition was necessary to account for variability in preexercise warm-up times and physiologic variability.

STATA 15 software (StataCorp, College Station, TX) was used for all statistical analyses. This trial is registered on ClinicalTrials.gov, identifier NCT02862730.

## RESULTS

### Primary Outcomes

Controlling the false discovery rate at 0.05, we calculated an adjusted threshold of $P < 0.0145$ to evaluate the statistical significance of the primary and secondary outcomes in Table 2. The mean (SD) percentage time in hypoglycemia during the exercise period, defined as the start of exercise until the start of the next meal, was the lowest with the dual-hormone system: 3.4% (4.5) compared with 8.3% (12.6) for the single-hormone system ($P < 0.009$) and 7.6% (8.0) for the predictive low glucose suspend system ($P < 0.001$) (Table 2). Median values are shown in Supplementary Fig. 3. The mean (SD) percentage time in hypoglycemia during the entire study was also the lowest with the dual-hormone system, with a mean time of 1.3% (1.0) compared with 2.8% (1.7) with the single-hormone system ($P < 0.001$), 2.0% (1.5) with the predictive low glucose suspend system ($P = 0.04$), and 3.1% (1.5) with current care ($P = 0.007$). Figure 1 compares the interquartile glucose plots of each study arm during the exercise and postexercise period, showing how hypoglycemia occurred more often with single-hormone than with dual-hormone. There was no statistical difference in the mean (SD) percentage time in hypoglycemia using the dual-hormone system compared with current care during the exercise period (3.4% [4.5] vs. 4.3% [6.8], $P = 0.49$). Current care was the only arm whereby participants were allowed to make adjustments to premeal bolus amounts and basal rates in anticipation of exercise. No snacks were provided before exercise in any of the arms.

Figure 2 shows the improvement in percentage time in range for single-hormone and dual-hormone arms compared with predictive low glucose suspend and current care arms of the study for the 20 participants who completed all study arms. The single-hormone system resulted in the highest time in range (70–180 mg/dL), with a mean time of 74.3 ± 8.0% across the 4 study days, which was similar to the mean time of 72.0 ± 10.8% with the dual-hormone system ($P = 0.44$). The time in range was lower with the predictive low glucose suspend system (65.2 ± 13.5%, $P = 0.036$ vs. dual-hormone) and was the lowest with current care (63.1 ± 17.3%, $P = 0.01$ vs. dual-hormone).

### Secondary Outcomes

In the context of high physical activity, participants received a mean glucagon dose of 510 μg/day. This amount was reduced to 348.2 μg/day when participants were not physically active. The amount of glucagon given during the 90-min period after the start of exercise was modestly lower on day 1 compared with day 4 (202 μg vs. 226 μg, $P = 0.22$). The median time from exercise start until the first delivery of glucagon was 35 min (interquartile range, 25–45) on day 1 and 22.5 min (interquartile range, 12.5–40) on day 4 after the algorithm adapted based on day 1 hypoglycemia ($P = 0.07$). The amount of insulin dosed per day was similar across all four study arms. The number of carbohydrate treatments for hypoglycemia was the lowest with the dual-hormone system, with a mean (SD) of 0.8 (0.7) treatments per day compared with 1.7 (1.4) with the single-hormone system ($P = 0.004$), 1.3 (1.3) with the predictive low glucose suspend system ($P = 0.065$), and 1.5 (1.2) with current care ($P = 0.10$).

The exercise detection algorithm had a sensitivity of 0.95 and a specificity of 0.99 during both single-hormone and dual-hormone arms of the study. Of 125 total exercise events recorded during these study arms, the algorithm detected 119 of them correctly. The exercise detection also identified 1.2 events each day when the participant was not doing the formal 45 min of aerobic exercise but METs exceeded the threshold for exercise detection.

Glucose sensor accuracy, calculated as mean absolute relative difference compared with the reference CBG values, was 10.5% (for reference >75 mg/dL), and the mean absolute difference was 10.8 mg/dL (reference ≤75 mg/dL).

The dual-hormone system was active and dosing insulin/glucagon automatically an average of 98.7% of the time.

**Table 2—Comparisons of the dual-hormone system, single-hormone system, predictive low glucose suspend system, and current care**

| End point | DH | SH | PLGS | CC | SH- DH | $P^1$ | PLGS-DH | $P^1$ | CC-DH | $P^1$ |
|---|---|---|---|---|---|---|---|---|---|---|
| % time in hypoglycemia (CGM <70 mg/dL) | | | | | | | | | | |
| Entire study | 1.3 (1.0) | 2.8 (1.7) | 2.0 (1.5) | 3.1 (3.2) | 1.5 | **<0.001** | 0.7 | 0.044 | 1.8 | **0.007** |
| Start of exercise in clinic until next meal | 3.4 (4.5) | 8.3 (12.6) | 7.6 (8.0) | 4.3 (6.8) | 4.9 | **0.009** | 4.3 | **<0.001** | 0.9 | 0.49 |
| % time in range (CGM 70–180 mg/dL) | | | | | | | | | | |
| Entire study | 72.0 (10.8) | 74.3 (8.0) | 65.2 (13.5) | 63.1 (17.3) | 2.4 | 0.44 | −6.5 | 0.036 | −8.8 | **0.010** |
| Start of exercise in clinic until next meal | 84.3 (16.7) | 83.3 (16.7) | 78.3 (18.9) | 78.2 (26.2) | −0.7 | 0.85 | −5.4 | 0.24 | −5.9 | 0.30 |
| Secondary end points: overnight (12 A.M.–6 A.M.) | | | | | | | | | | |
| % time in hypoglycemia (CGM <70 mg/dL) | 0.6 (2.1) | 1.6 (6.2) | 0.8 (3.7) | 4.5 (11.9) | 1.0 | 0.30 | 0.0 | 0.98 | 3.8 | **0.007** |
| % time in range (CGM 70–180 mg/dL) | 80.1 (29.5) | 80.8 (28.9) | 62.9 (36.1) | 57.9 (40.6) | 1.0 | 0.88 | −16.6 | **0.001** | −22.0 | **<0.001** |
| Mean sensed glucose (mg/dL) | 149 (38) | 145 (31) | 170 (49) | 164 (62) | −5 | 0.53 | 20 | **0.002** | 14 | 0.019 |
| Secondary end points: entire study period | | | | | | | | | | |
| Mean sensed glucose (mg/dL) | 155 (16) | 148 (12) | 162 (20) | 161 (28) | −8 | 0.062 | 7 | 0.12 | 6 | 0.29 |
| % time CGM <54 mg/dL[2] | 0.3 (0.4) | 0.6 (0.6) | 0.2 (0.3) | 0.4 (0.6) | 0.4 | **0.010** | 0.0 | 0.69 | 0.1 | 0.39 |
| % time CGM >180 mg/dL | 26.7 (11.3) | 22.9 (8.7) | 32.8 (13.9) | 33.7 (18.1) | −3.9 | 0.23 | 5.9 | 0.066 | 7.0 | 0.054 |
| % time CGM >250 mg/dL | 6.0 (4.0) | 3.3 (3.0) | 8.3 (7.7) | 8.7 (12.2) | −2.7 | **0.003** | 2.1 | 0.22 | 2.6 | 0.27 |
| Carbohydrate treatments per day,[3],[4] *n* | 0.8 (0.7) | 1.7 (1.4) | 1.3 (1.3) | 1.5 (1.2) | 2.3 | **0.004** | 1.6 | 0.065 | 1.8 | **0.010** |
| Events with CBG <70 mg/dL,[3] *n* | 0.7 (1.5) | 1.1 (0.7) | 0.8 (0.7) | 0.9 (1.0) | 1.7 | **0.004** | 1.2 | 0.53 | 1.2 | 0.38 |
| Events with CBG <54 mg/dL,[5] *n* | 0.1 (0.2) | 0.2 (0.3) | 0.1 (0.1) | 0.2 (0.3) | | | | | | |
| Insulin per day (units) | 43.6 (15.5) | 43.0 (14.6) | 42.8 (17.9) | 44.0 (13.7) | −0.8 | 0.51 | −1.1 | 0.52 | 0.3 | 0.86 |
| Glucagon per day (μg) | 510 (207) | | | | | | | | | |

Data are mean (SD) unless otherwise indicated. CC, current care; DH, double-hormone system; PLGS, predictive low glucose suspend; SH, single-hormone system. [1]Statistical significance evaluated using threshold of 0.0145 to control false discovery rate at a total level of 0.05 across all tests. Bold values are statistically significant. [2]Bootstrapped hypothesis tests. [3]Differences expressed as ratios. [4]Weighted to reflect a 24-h day, although actual observation time may have been shorter. [5]Too few events to test.

The single-hormone system and predictive low glucose suspend systems were active 98.7% and 95.5% of the time, respectively. The total time observed ranged from 81 to 87 h, with a mean (SD) of 82.8 (0.86) h.

### Intention-to-Treat Analysis

An intention-to-treat analysis, including the data from the five participants who did not complete all four study arms, did not alter our conclusions (see Supplementary Table 1). Similarly, omitting outliers did not alter our conclusions (see Supplementary Table 2).

### Adverse Events

There were 31 adverse events during the study (see Supplementary Table 3). The most common adverse event was gastrointestinal upset, which was experienced by five participants in the dual-hormone arm, three in the predictive low glucose suspend arm, and one in the current care arm. All events resolved without sequelae, and none were classified as serious.

## DISCUSSION

Here we describe a novel automated exercise-enabled dual-hormone closed-loop system that outperformed an exercise-enabled single-hormone system and a predictive low glucose suspend system in hypoglycemia reduction, demonstrating the value of glucagon in glucose management during exercise. Our previous inpatient study (5) demonstrated that for a dual-hormone system, including an exercise announcement reduced the time in hypoglycemia compared with a dual-hormone system that did not adjust dosing during exercise. The current study described here provides new information because it includes automated exercise detection, home use of these systems, and compares an exercise-enabled dual-hormone system to a single-hormone exercise-enabled system, to a predictive low glucose suspend system, and to current care.

El-Khatib et al. (17) recently published their outpatient experience with a dual-hormone system over 11 days without structured exercise. Use of the dual-hormone system reduced absolute time in hypoglycemia (<60 mg/dL) by 1.3% compared with usual care (17). Haidar et al. (6,18) compared a dual-hormone to a single-hormone system overnight in children attending a diabetes camp and a second overnight study including exercise. No statistically significant differences were found in time in hypoglycemia between the dual-hormone and single-hormone systems. In contrast, Taleb et al. (19) demonstrated a significant reduction in hypoglycemia using a dual-hormone system compared with a single-hormone system over 90 min when exercise was announced 20 min before exercise, resulting in preemptive shut off of the basal insulin.

The use of single-hormone systems to reduce exercise-related hypoglycemia has been described by multiple groups, including Sherr et al. (20). The single-hormone system in their study significantly decreased nocturnal hypoglycemic events but did not affect hypoglycemic events during exercise. Participants were given carbohydrate before exercise for glucose <120 mg/dL. Participants in our study were not given carbohydrate before exercise because doing so would have masked the true rate of hypoglycemia. In addition, many people exercise to lose weight or to maintain a healthy

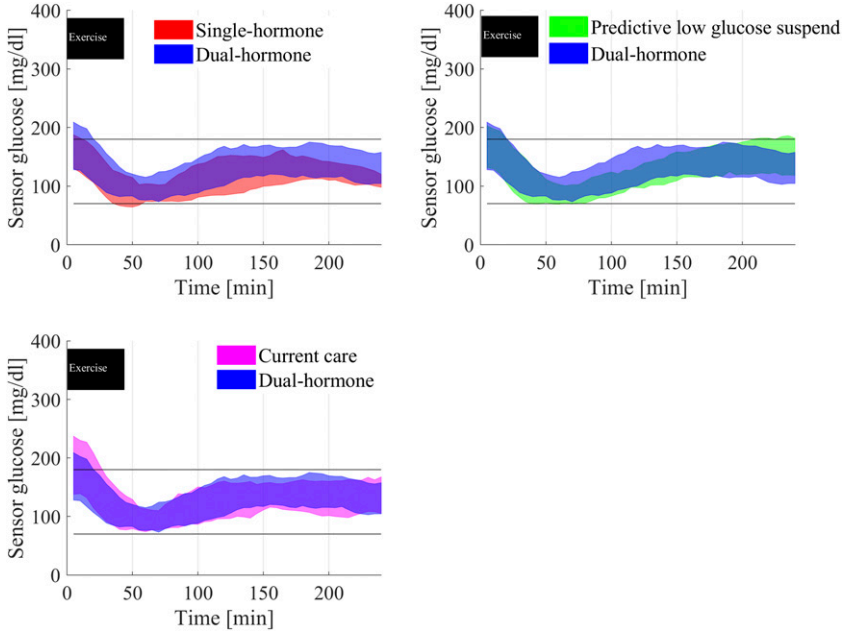


**Figure 1**—Glucose from the start of exercise to 4 h after exercise. The 25% and 75% interquartile ranges are shown. The upper black line indicates 180 mg/dL and the lower black line indicates 70 mg/dL. Note that the dual-hormone system resulted in reduced hypoglycemia and a higher minimum glucose level compared with the single-hormone system.

weight, an important consideration given the high rates of obesity in type 1 diabetes (21). Breton et al. (22) described the use of a model-based single-hormone system in adolescents skiing/snowboarding. Time in hypoglycemia was reduced by 1.4% with the use of the single-hormone system compared with open-loop, with 3.4 carbohydrate treatments per day given on average during single-hormone use.

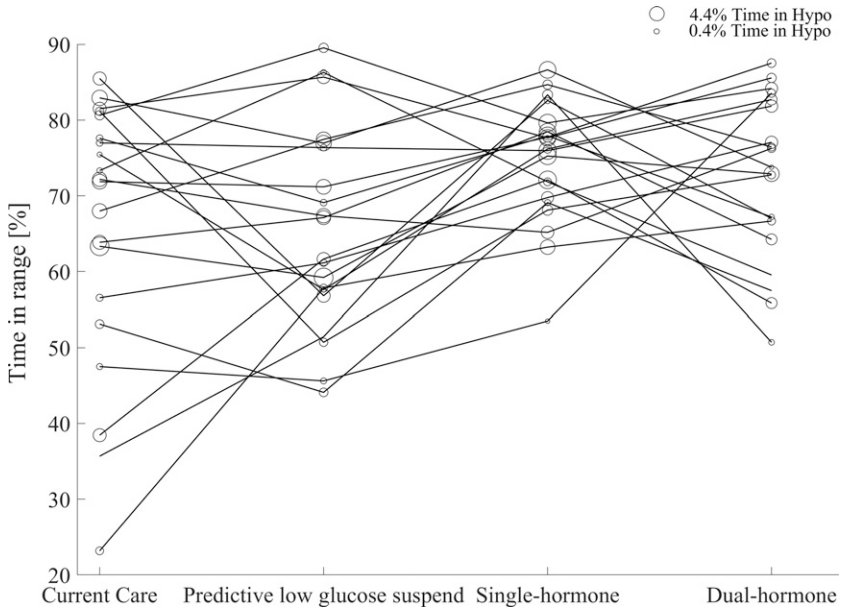


**Figure 2**—Percentage of time within target range across the four arms of the study for the 20 participants who completed all study arms. Each participant is represented by a line. The percentage of time in range (CGM 70–180 mg/dL) is graphed on the *y*-axis across each study arm. The time in hypoglycemia (CGM <70 mg/dL) is noted by the size of each circle. The single-hormone and dual-hormone systems resulted in more time within the target range, with more heterogeneity of time in range under current care. The dual-hormone system also resulted in less time in hypoglycemia.

Breton et al. (23) also described using elevated heart rate to detect exercise and modify insulin dosing. This method reduced the rate of glucose decline but not hypoglycemia. In a second study using heart rate (24), heart rate input improved hypoglycemia but not to the level of statistical significance. Similarly, Huyett et al. (25) found that Zone Model Predictive Control reduced time in hypoglycemia, but the reduction did not reach statistical significance. Turksoy et al. (26) incorporated exercise detection as a component of a single-hormone system using the SenseWear armband. Doing so eliminated hypoglycemia in the latter three subjects but required subjects to ingest carbohydrates, and the avoidance of hypoglycemia was often at the expense of hyperglycemia.

Participants in the current care arm of our study were allowed to make insulin adjustments before exercise. With these adjustments, the current care arm had a low rate of hypoglycemia. This finding highlights the importance of patient education to prevent hypoglycemia. A recently published consensus statement provided much needed guidance on best practices to reduce exercise-related dysglycemia (27). The challenge is that patients often forget to make these adjustments or exercise is not scheduled in advance, which is why the development of automated systems is critical for patient safety and to reduce disease burden.

The benefit of glucagon may be overstated in a study if the single-hormone system performs poorly. However, the time in range for the single-hormone system in this study of 74.3% is similar to the 70.8% reported for single-hormone systems in a recent meta-analysis of closed-loop studies (28). The insulin delivery algorithm was identical between the single-hormone and dual-hormone system in this study. The differences in glycemic outcomes between the two systems are therefore attributable to glucagon delivery. The dual-hormone system significantly reduced but did not completely eliminate hypoglycemia. This is an important consideration given the additional cost and complexity associated with including glucagon (29) as well as the risk of adverse effects, including nausea. Glucagon is also known to have effects on many systems and organs (30). Although repeated glucagon doses over 16 h were not shown to cause significant declines in hepatic glycogen (31), there is a risk of glycogen depletion in patients that are not eating regularly. Overdelivery of

glucagon can also lead to hyperglycemia. There was a small but significant increase in time in hyperglycemia (>250 mg/dL) with the use of the dual-hormone system compared with the single-hormone system in our study, although it was not higher than the other two arms. The safety of chronic glucagon delivery in humans needs to be established before commercialization of dual-hormone systems, and the dose of glucagon should be kept as low as possible. Glucagon was given earlier on day 4 than on day 1 due to the adaptation of the algorithm that occurred based on day 1 hypoglycemia. However, glucagon was still not given until a median of 22.5 min into exercise. Giving glucagon earlier may have reduced hypoglycemia event further, an area that requires further study.

Commercially available glucagon is Food and Drug Administration–approved for use only immediately after reconstitution. This study was conducted under an investigational device exemption that allowed for use of reconstituted glucagon over 24 h, an approach supported by Taleb et al. (32). A stable glucagon formulation to enable longer-term use is not yet commercially available, although multiple formulations are in development (33,34). In addition, dual-chambered pumps or pods are needed to make delivery of both insulin and glucagon practical.

The dual-hormone system in this study included a modification of the glucagon delivery once exercise was detected and also an adaptive component. Although the glucose target for insulin delivery was not adjusted during exercise, adaptation was not needed because insulin delivery was completely stopped for the first 30 min after exercise was detected and then reduced by 50% for the subsequent hour. This approach is similar to raising the glucose target but has the advantage of shutting off insulin rapidly. Modifications to insulin/glucagon delivery were only implemented by the algorithm if the patient confirmed exercise by hitting the acknowledgment button. For safety, the system does not allow for implementation of the exercise modifications if the glucose is >250 mg/dL.

Exercise is challenging to manage in type 1 diabetes, partly because there are many types of exercise to consider and each type affects glucose metabolism in different ways (35,36). Our study was limited in that the in-clinic exercise sessions consisted of a single type of activity, intensity, and duration. Participants did complete at least one at-home exercise session per arm to test these systems across a larger variety of activities. The activities were self-selected and included walking, yard work, dancing, hiking, sledding, and snowboarding. In this study, the exercise detection algorithm detected 95% of the exercise events accurately, but there were an average of 1.2 events/day when exercise was detected but declined by the user. Participants were asked not to confirm exercise if it was not a formal exercise event. This meant, for example, a brisk walk that exceeded 4 METs was logged as a false positive. It may have been appropriate to adjust dosing in these instances, an area that requires further study.

Another limitation of this study was the dropout rate. The intention-to-treat analysis provided very similar results to the final data analysis, which indicates that the dropout rate did not likely affect the final study results. Lastly, participants were remotely monitored for the duration of the study, with the exception of the current care arm because these participants were blinded to the study CGM. This monitoring was done for safety because this was the first test of these systems in the outpatient setting and may not be required in the future. People with a history of recent severe hypoglycemia or hypoglycemia unawareness were excluded. These patients may have the most to benefit from dual-hormone systems, and further studies are required to assess the safety of these systems in this at-risk population.

## CONCLUSIONS

We have shown that an exercise-enabled dual-hormone system can significantly reduce hypoglycemia after aerobic exercise. The use of glucagon increases system complexity and cost, and some participants experienced nausea. Glucagon delivery may need to be timed earlier in exercise to prevent hypoglycemia and at a lower dose to reduce the risk of adverse effects. We have further shown that a single-hormone system also performs well, but a snack or an earlier exercise announcement may be needed to avoid exercise-related hypoglycemia.

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