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.
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.

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.

Table 1—Baseline characteristics

| Characteristic          | Values          |
|-------------------------|-----------------|
| Age (years)             | 34.5 (4.7)      |
| Weight (kg)             | 77.4 (16.0)     |
| Sex                     | Male Female     |
|                         | 9 16            |
| HbA1c (%)               | 7.5 (0.9)       |
| HbA1c (mmol/mol)        | 58 (9.8)        |
| Diabetes duration (years)| 20.2 (8.9)     |
| CGM users               | 13              |

Data are mean (SD) or n.
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 CGM 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 AM (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 α 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 exercise warm-up times and physiologic variability.

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 1.2 (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.
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 98.7% and 95.5% of the time, respectively.

**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.

**CONCLUSIONS**
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 weight.
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. 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, sledging, 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.

Conclusion
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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Duality of Interest. J.R.C. and P.G.J. have a financial interest in Pacific Diabetes Technologies, a company that may have a commercial interest in the results of this research and technology. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. J.R.C., J.E.Y., L.M.W., and P.G.J. contributed to the writing, literature search, study design, data collection, data analysis, data interpretation, closed-loop system construction, and figures. R.R., N.R., and J.L. contributed to the data analysis, data collection, closed-loop system construction, and figures. D.B., U.R., B.S., S.M.S., and L.G. contributed to the data collection and tables. K.R. contributed to the statistical analysis and tables. J.R.C. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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References
1. Thabt H, Hovorka R. Coming of age: the artificial pancreas for type 1 diabetes. Diabetologia 2016;59:1795–1805
2. Heinemann L, Muchmore D. Coverage of prandial insulin requirements: an elusive goal. Diabetes Technol Ther 2017;19:7–8
3. McMahon SK, Ferreira LD, Ratnam N, et al. Glucose requirements to maintain euglycemia after moderate-intensity afternoon exercise in adolescents with type 1 diabetes are increased in a biphasic manner. J Clin Endocrinol Metab 2007;92:963–968
4. Castle JR, England JA, ElYousselj J, et al. Novel use of glucagon in a closed-loop system for prevention of hypoglycemia in type 1 diabetes. Diabetes Care 2010;33:1282–1287
5. Jacobs PG, El Yousselj J, Reddy R, et al. Randomized trial of a dual-hormone artificial pancreas with dosing adjustment during exercise compared with no adjustment and sensor-augmented pump therapy. Diabetes Obes Metab 2016;18:1110–1119
6. Haidar A, Legault L, Matteau-Pelletier L, et al. Outpatient overnight glucose control with dual-hormone artificial pancreas, single-hormone artificial pancreas, or conventional insulin pump therapy in children and adolescents with type 1 diabetes: an open-label, randomised controlled trial. Lancet Diabetes Endocrinol 2015;3:595–604
7. van Bon AC, Liif YM, Koeburger R, Koops R, Hoekstra J, DeVries JH. Feasibility of a portable bionic closed-loop system to control glucose excursions at home under free-living conditions for 48 hours. Diabetes Technol Ther 2014;16:131–136
8. Russell SJ, Hillard MA, Balliro C, et al. Day and night glycemic control with a bionic pancreas versus conventional insulin pump therapy in preadolescent children with type 1 diabetes: a randomised crossover trial. Lancet Diabetes Endocrinol 2016;4:233–243
9. Taborsky GJ Jr. The physiology of glucagon. J Diabetes Sci Technol 2010;4:1338–1344
10. Jacobs PG, Resalat N, El Youssef J, et al. Incorporating an exercise detection, grading, and hormone dosing algorithm into the artificial pancreas using accelerometer and heart rate. J Diabetes Sci Technol 2015;9:1175–1184
11. Jacobs PG, El Youssef J, Castle J, et al. Automated control of an adaptive bihormonal, dual-sensor artificial pancreas and evaluation during inpatient studies. IEEE Trans Biomed Eng 2014;61:2569–2581
12. Zhong A, Choudhary P, McMahon C, et al. Effectiveness of automated insulin management features of the MiniMed® 640G sensor-augmented insulin pump. Diabetes Technol Ther 2016;18:657–663
13. Agiostratidou G, Anhalt H, Ball D, et al. Standardizing clinically meaningful outcome measures beyond HbA1c for type 1 diabetes: a consensus report of the American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes Association, the Endocrine Society, JDRF International, The Leona M. and Harry B. Helmsley Charitable Trust, the Pediatric Endocrine Society, and the T1D Exchange. Diabetes Care 2017;40:1622–1630
14. Maahs DM, Buckingham BA, Castle JR, et al. Outcome measures for artificial pancreas clinical trials: a consensus report. Diabetes Care 2016;39:1175–1179
15. Simes RJ. An improved Bonferroni procedure for multiple tests of significance. Biomетrika 1986;73:751–754
16. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc Series B Stat Methodol 1995;57:289–300
17. El-Khatib FH, Balliro C, Hillard MA, et al. Home use of a bihormonal bionic pancreas versus insulin pump therapy in adults with type 1 diabetes: a multicentre randomised crossover trial. Lancet 2017;389:369–380
18. Haidar A, Rabasa-Lhoret R, Legault L, et al. Single- and dual-hormone artificial pancreas for overnight glucose control in type 1 diabetes. J Clin Endocrinol Metab 2016;101:214–223
19. Taleb N, Emami A, Suppere C, et al. Efficacy of single-hormone and dual-hormone artificial pancreas during continuous and interval exercise in adult patients with type 1 diabetes: randomised controlled crossover trial. Diabetologia 2016;59:2561–2571
20. Sherr JL, Cengiz E, Palerm CC, et al. Reduced hypoglycaemia and increased time in target using closed-loop insulin delivery during nights with or without antecedent afternoon exercise in type 1 diabetes. Diabetes Technol Ther 2016;18:589–594
21. Miller KM, Foster NC, Beck RW, et al.; T1D Exchange Clinic Network. Current state of type 1 diabetes treatment in the U.S.: updated data from the T1D Exchange clinic registry. Diabetes Care 2015;38:971–978
22. Breton MD, Cherniavsky DR, Forlenza GP, et al. Closed-loop control during intense prolonged outdoor exercise in adolescents with type 1 diabetes: the artificial pancreas ski study. Diabetes Care 2017;40:1644–1650
23. Breton MD, Brown SA, Karvetski CH, et al. Adding heart rate signal to a control-to-range artificial pancreas system improves the protection against hypoglycaemia during exercise in type 1 diabetes. Diabetes Technol Ther 2014;16:506–511
24. DeBoer MD, Cherniavsky DR, Topchyan K, Kovatchev BP, Francis GL, Breton MD. Heart rate informed artificial pancreas system enhances glycemic control during exercise in adolescents with T1D. Pediatr Diabetes 2017;18:540–546
25. Huyett LM, Ly TT, Forlenza GP, et al. Outpatient closed-loop control with unannounced moderate exercise in adolescents using zone model predictive control. Diabetes Technol Ther 2017;19:331–339
26. Turksoy K, Quinn LT, Littlejohn E, Cinar A. An integrated multivariable artificial pancreas control system. J Diabetes Sci Technol 2014;8:498–507
27. Riddell MC, Gallen IW, Smart CE, et al. Exercise management in type 1 diabetes: a consensus statement. Lancet Diabetes Endocrinol 2017;5:377–390
28. Weisman A, Bai JW, Cardinez M, Kramer CK, Perkins BA. Effect of artificial pancreas systems on glycemic control in patients with type 1 diabetes: a systematic review and meta-analysis of outpatient randomised controlled trials. Lancet Diabetes Endocrinol 2017;5:501–512
29. Haidar A, Smaoui MR, Legault L, Rabasa-Lhoret R. The role of glucagon in the artificial pancreas. Lancet Diabetes Endocrinol 2016;4:476–479
30. Taleb N, Haidar A, Messier V, Gingras V, Legault L, Rabasa-Lhoret R. Glucagon in artificial pancreas systems: potential benefits and safety profile of future chronic use. Diabetes Obes Metab 2017;19:13–23
31. Castle JR, El Youssef J, Bakhtiani PA, et al. Effect of repeated glucagon doses on hepatic glycogen in type 1 diabetes: implications for a bihormonal closed-loop system. Diabetes Care 2015;38:2115–2119
32. Taleb N, Coriati A, Khazzaka C, Bayonne J, Messier V, Rabasa-Lhoret R. Stability of commercially available glucagon formulation for dual-hormone artificial pancreas clinical use. Diabetes Technol Ther 2017;19:589–594
33. Castle JR, Youssef JE, Branigan D, et al. Comparative pharmacokinetic/pharmacodynamic study of liquid stable glucagon versus lyophilized glucagon in type 1 diabetes subjects. J Diabetes Sci Technol 2016;10:1101–1107
34. Hövelmann U, Bysted BV, Mouritzen LJ, et al. Pharmacokinetic and pharmacodynamic characteristics of dasiglucagon, a novel soluble and stable glucagon analog. Diabetes Care 2018;41:531–537
35. García-García F, Kumareswaran K, Hovorka R, Hernando ME. Quantifying the acute changes in glucose with exercise in type 1 diabetes: a systematic review and meta-analysis. Sports Med 2015;45:587–599
36. Bussau VA, Ferreira LD, Jones TW, Fournier PA. The 10-s maximal sprint: a novel approach to counter an exercise-mediated fall in glycaemia in individuals with type 1 diabetes. Diabetes Care 2006;29:601–606