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Randomized trial of a dual-hormone artificial pancreas with dosing adjustment during exercise compared with no adjustment and sensor-augmented pump therapy

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Abstract

Aims—Exercise increases risk of hypoglycemia in type 1 diabetes (T1D). An artificial pancreas (AP) can help mitigate this risk. We tested whether adjusting insulin and glucagon in response to exercise within a dual-hormone AP reduces exercise-related hypoglycemia.

Materials and Methods—In random order, 21 adults with T1D underwent three 22 h sessions: AP with exercise dosing adjustment (APX), AP with no exercise dosing adjustment (APN), and sensor-augmented pump therapy (SAP). After an overnight stay and 2 hours after breakfast, participants exercised for 45 minutes at 60% of their maximum heart rate with no snack given before exercise. During APX, insulin was decreased and glucagon was increased at exercise onset, while during SAP, subjects could adjust dosing before exercise. The two primary outcomes were percent of time in hypoglycemia (<3.9 mmol/L) and percent of time in euglycemia (3.9–10 mmol/L) from the start of exercise to the end of the study.

Results—The mean times spent in hypoglycemia (<3.9 mmol/L) after the start of exercise were 0.3% [−0.1, 0.7%] for APX, 3.1% [0.8, 5.3%] for APN, and 0.8% [0.1, 1.4%] for SAP. There was an absolute difference of 2.8% less time in hypoglycemia in APX versus APN ($p = 0.001$) and 0.5% less time in hypoglycemia for APX versus SAP ($p = 0.16$). Mean time in euglycemia was comparable across conditions.

Conclusions—Adjusting insulin and glucagon delivery at exercise onset within a dual-hormone AP significantly reduces hypoglycemia compared with no adjustment and performs similarly to SAP when insulin is adjusted before exercise.

Introduction

Optimal glucose control in persons with diabetes is essential to prevent potentially life-threatening complications. Diabetes is the leading cause of kidney failure, non-traumatic lower-limb amputations, and new cases of blindness among working-aged adults in the United States (1). Those with type 1 diabetes, who have little or no insulin secretion and dysfunctional glucagon secretion, are at high risk for both hyperglycemia and hypoglycemia. Due to the difficulty of managing diabetes, there is ongoing research to develop an artificial endocrine pancreas (AP) system. Such a system is comprised of a glucose sensor from which data are collected and streamed into an algorithm (run on a smart-phone) which in turn controls delivery from an insulin pump.

Significant progress has been made in the area of the artificial pancreas (AP) recently leading to successful long-term usage within the homes of people with type 1 diabetes (T1D). Hovorka et al. recently showed that for people with T1D, glucose control could be improved when using a single-hormonal AP system for 12 weeks under free living conditions compared with sensor-augmented pump (SAP) therapy (2) in a randomized multicenter cross-over trial. Kropff et al. also recently published results from a long-term single-hormone study showing that when patients with T1D used an AP during evening hours and while sleeping, time spent in euglycemia increased and A1C dropped modestly compared with participants who used SAP 24-hours per day (3). Dual-hormone APs that deliver glucagon as well as insulin have also shown promise by our group (4) and others, especially in helping to prevent hypoglycemia (5). Russell et al. showed how use of a dual-hormonal AP could improve time spent in euglycemia and reduce time spent in hypoglycemia and hyperglycemia (6).

Exercise has been a challenge to AP systems. During exercise, glucose levels can fall rapidly due to an increase in insulin sensitivity and the rapid uptake of glucose in muscles due to insulin-independent translocation of GLUT-4 and increased muscle blood flow during exercise (7). In normal physiology, insulin secretion is quickly ceased when blood glucose falls, and endogenous glucose production is increased due to an increase in glucagon and catecholamine secretion (8). In type 1 diabetes, insulin is given exogenously leading to a high risk of hypoglycemia, particularly after exercise. In a study of 48 children with type 1 diabetes who did not alter insulin delivery for exercise, glucose dropped by an average of 40% after 60 min of mild exercise (9). A total of 52% of the participants developed hypoglycemia (<3.9 mmol/L). In a follow up study by the DirecNet Study Group, when basal insulin was stopped at the start of exercise, 16% of patients still became hypoglycemic and 27% of patients became hyperglycemic (>11.1 mmol/L) (10). To estimate the optimal adjustment of insulin for exercise, Schiavon and Cobelli et al. utilized in silico simulations and found the optimal adjustment for the simulated population was to reduce basal rates by 50% for 90 min prior to exercise with a subsequent reduction of 30% during exercise (11). Patients commonly do not plan exercise 90 min in advance, which makes this type of

recommendation challenging for patients to follow. If insulin is not appropriately adjusted prior to exercise, hypoglycemia and even life-threatening hypoglycemia can result even hours after exercise is completed (12), which is in part due to the attenuation of the sympatho-adrenal response to hypoglycemia after exercise (13). As shown by McMahon et al. (14) in a study of 9 individuals with type 1 diabetes who underwent a euglycemic clamp while exercising for 45 minutes on a cycle ergometer and then resting for the remainder of the study, there was a sharp increase in the required glucose infusion rate during exercise, but also a significant increase again six hours later, which the authors theorized was related to repletion of muscle glycogen overnight. This delayed impact of exercise on glycemia is difficult for patients to compensate for and there remains an unmet need for advanced technologies to address this issue.

There have been multiple published studies on the topic of exercise and AP systems (15–19). In these studies, carbohydrates were commonly given prior to exercise to reduce the risk of hypoglycemia during and after exercise. There remains an unmet need to improve glucose control for persons with type 1 diabetes during exercise and better prevent exercise-related hypoglycemia. We present results from a randomized controlled cross-over experiment that shows the benefit of adjusting dosing in response to exercise. In addition to comparing with an AP that did not adjust dosing in response to exercise, we also compared with sensor-augmented pump therapy during which participants were aware of the exercise that they were going to do and were able to adjust dosing in advance of the exercise. The experimental results presented here provide evidence that detecting and responding to exercise is important for preventing exercise-induced hypoglycemia in a dual-hormone AP.

Materials and Methods

Study design and cohort

We performed a randomized three-way controlled, cross-over study comparing dual-hormone AP that adjusted insulin and glucagon dosing during and following exercise (APX), a dual-hormone AP that did not adjust dosing based on exercise (APN), and sensor-augmented pump (SAP) therapy. Each study period was 22 hours, which included an overnight stay, and was completed at the clinical research center at Oregon Health & Science University (Portland, OR). A washout period between the 22 hour sessions ranged from 7 to 42 days. The study was approved by the institutional review board at Oregon Health & Science University.

Participants

Participants were recruited from Portland, OR and the surrounding areas and were enrolled between January and September, 2015. All participants provided written informed consent prior to participating in the study. Participants were required to be between the ages of 18 and 45. Patients with prior history of cardiovascular, cerebrovascular, kidney, or liver disease, microvascular disease, autonomic neuropathy, or any other uncontrolled chronic medical conditions were excluded. Participants were interviewed by a physician and underwent a physical exam that included an EKG. Other exclusion criteria included oral or parenteral corticosteroid use, adrenal insufficiency, seizure disorder, immunosuppressant

use, insulin or glucagon allergies, hypoglycemia unawareness, C peptide level 0.5 mg/mL or insulin resistance requiring more than 200 units of insulin per day. Hypoglycemia unawareness was determined during an interview with the physician who asked questions about severe hypoglycemia over the past 12 months and questions about their ability to sense when their glucose fell below 3.3 mmol/L. All participants had previously used a continuous sensor and an insulin pump prior to the study and no additional training on SAP therapy was done. Participants used their own insulin pumps during SAP but each subject was given a Dexcom sensor to use.

Twenty-three participants were enrolled in the study between January and November 2015. Twenty-one participants completed all studies and were included in the data analysis (see Figure 1) and supplemental Table S1 for baseline characteristics of the participants.

Randomization and masking

Participants and investigators were aware of the assigned sequence order. Participants were masked to capillary blood glucose levels and insulin and glucagon infusion rates during the APN and APX study periods, but were not masked to sensor glucose or insulin infusion during the SAP study period. Using Excel (Microsoft, Redmond), we randomized treatment order in a replicated Latin squares design using blocks of six possible sequences designed to balance both the period effect (whether the treatment came first, second, or third) and sequence effect (which treatments it preceded/followed). The original randomization order was for 8 participants to complete open loop therapy first, 7 participants to complete closed loop therapy first and for 8 participants to complete closed loop with exercise announcement first. Due to an error, one participant randomized to complete APN first completed APX first instead.

Procedures

At the screening visit, after written informed consent was obtained, study staff reviewed the participant's medical history and medications including insulin dosing, performed a physical examination, drew blood for measurement of A1C, complete metabolic panel, complete blood count, C-peptide, and if applicable, performed a urine pregnancy test. A maximal cardiopulmonary EKG stress test with maximal oxygen uptake (VO_{2max}) was performed following a standard Bruce Protocol on a Medtrack ST 55 treadmill ergometer. Participants exercised to maximum achieving a respiratory exchange ratio (RER) above 1.1 which meets the criteria for a valid maximal exercise test (20).

For each of the three arms of the study, enrolled participants arrived at the clinical research center at 7 PM on day 1 and concluded the study at 5 PM on day 2. Participants consumed a low-carbohydrate breakfast (20–30 g) at 6 AM on the second day and then exercised on a treadmill ergometer (Medtrack ST55) for 45 minutes at 60% of their maximum heart rate 2 hours after completing breakfast. Participants consumed a self-selected lunch 3 hours after exercise and were discharged five hours later. All meals were identical between visits for individual subjects. Meals were prepared by the OHSU Bionutrition department. Any unconsumed food was weighed back so that on the subsequent visits, the subject was given the exact same amount of food as they had consumed previously.

The AP system used in this study was comprised of (1) a Google Nexus phone (Google Inc., Mountain View) running custom control and graphical user interface software(4), (2) two t:slim pumps (Tandem, San Diego), one filled with Novolog insulin (Novo Nordisk, Plainsboro), and one filled with GlucaGen glucagon (Novo Nordisk, Plainsboro), (3) a Dexcom G4 AP Share glucose sensor (Dexcom, San Diego) (4) a back-up rechargeable 3500 mAh battery (Zero Lemon, Hong Kong), (5) a custom 3-D printed enclosure that integrated the Dexcom receiver with the smart phone, and (6) a cloud storage, alert, and reporting platform for reporting results to clinicians during and after a study. The Dexcom sensors were placed 24–72 h prior to the intervention visits and were calibrated every 12 h.

The AP control algorithm used in both AP visits is a modified proportional-integral-derivative algorithm as described previously (4). The exercise dosing adjustment algorithm used in APX and its development have been described in a prior publication (21). This dosing adjustment reduced insulin and increased glucagon during and after exercise for 1.5 hours after the start of exercise. No insulin was delivered for 30 minutes after the start of exercise, and the AP insulin dosage was reduced by 50% during the subsequent hour. The glucagon dosage was increased by a factor of two for 90 minutes after the start of exercise. The settings for the insulin and glucagon dosing in response to exercise were selected and optimized based on in-silico testing described previously (21). Initiation of the APX dosing algorithm was announced to the AP by having the patient press a button on the phone. For all study sessions, if participants' blood glucose levels dropped below 3.9 mmol/L, they were given 15 g of rescue carbohydrates.

Outcomes

The pre-determined primary outcomes were based on sensed glucose and were the percent of time in hypoglycemia (<3.9 mmol/L) and percent of time in euglycemia (3.9 – 10 mmol/L) from the start of exercise until the end of the study. Secondary outcome measures were mean sensed glucose, number of carbohydrate treatments, percent of time with: sensed glucose <2.8 mmol/L, >10 mmol/L, and number of events with capillary blood glucose (CBG) <2.8 and <3.9 . We defined a single hypoglycemic event as starting when a CBG measurement went below the threshold and ending with the next CBG measurement above the threshold. As determined a priori, the secondary outcomes were assessed over the entire study period excluding the first 4 hours of the study to enable the AP system to stabilize.

Statistical analysis

In our power calculation, we postulated that APX treatments would reduce time in hypoglycemia relative to SAP by 33 minutes ($SD=50$), or approximately 3.3% (SD 5%) of observation time. We used a paired t-test to approximate the planned paired mean comparisons and calculated that 21 participants would provide 80% power at the 5% significance level to detect a difference between APX conditions and SAP. A sample size of 34 achieves 81% power to detect a mean paired difference in time in hypoglycemia between APX and APN of 15 minutes ($SD=30$) and with a significance level (α) of 0.05 using a two-sided paired t-test.

A total of 21 participants completed all three studies and were included in the data analysis. We modeled the relationship between each outcome and study arm using generalized estimating equations (GEE) to account for correlation between repeated observations. We included an effect for period in sequence to control for possible carryover or learning effects. Percent of time in hypoglycemia, euglycemia, and hyperglycemia were modeled as proportions using a normal generalized linear regression model; because some estimates were very close to zero, we modeled the log mean with a log link to constrain estimates to be between 0 and 1, and used robust (empirical) variance to correct departures from normality. We used Poisson regression for count outcomes (hypoglycemic events and rescue treatments). We were unable to model percent of time with capillary blood glucose <2.8 mmol/L as planned because too few of these events occurred and models would not converge; instead, we tested paired mean differences with the nonparametric Wilcoxon signed-rank test. For mean insulin, glucagon, and glucose we used linear regression models. Stata version 13 (StatCorp LP, College Station) was used for all statistical analyses.

This study is registered on clinicaltrials.gov, identifier NCT02241889.

Results

Including an exercise dosing adjustment within an AP (APX) significantly reduced the percentage of time spent in hypoglycemia compared with no adjustment (0.3% with APX versus 3.1% with APN, absolute difference of 2.8% less time in hypoglycemia with APX, see Table 1). There was no statistically significant difference in the baseline glucose of APN and APX (Table 1). The difference in hypoglycemia primarily occurred after exercise had ended (see plot of interquartile ranges in Figure 2). For APN, there was one case when CBG fell below 2.8 mmol/L, and no such extreme hypoglycemic episodes for APX.

Figure 3 shows control variability plots under SAP, APN, and APX for the entire study duration minus the first 4 hours of the study. Each dot on the graph represents the minimum (x-axis) and maximum (y-axis) sensor reading for each participant during the test period. The control variability graph shows that more hyperglycemia occurred during the SAP trial as shown by the data appearing in the E Zone. While hyperglycemia was reduced under the APN arm compared with the SAP and the APX arms, hypoglycemia occurred more often with data appearing in the Lower D region including significant hypoglycemia (<2.8 mmol/L). The APX arm of the study eliminated the significant hypoglycemia events.

Supplemental Figure S1 shows a plot of the interquartile range (25% to 75%) across all participants and 95% range for the APX trial compared with the SAP trial for the entire duration minus the first 4 hours of settling time. Figure S1 further shows how the APX system tended to moderately reduce variability and narrow the range of glucose control while also preventing extreme hypoglycemia and hyperglycemia from occurring as compared with SAP trials, especially during the overnight period (Table S2). During the overnight period, participants in OL had an average standard deviation of 2.0 mmol/L [1.7, 2.4] while for subjects in APX, the average standard deviation was 1.6 mmol/L [1.3, 1.9], which was trending towards significant ($p=0.07$). Increased hyperglycemia was observed in APX compared with APN when considering the entire study duration (Table 1). To consider

whether this was a result of exercise, we looked at the percent time in hyperglycemia between APX and APN across three windows: (1) during the overnight period, (2) during the time immediately after the start of exercise to lunch, and (3) from lunch to the end of the experiment. Overnight, participants during APX had a higher percent time in hyperglycemia at 17.2% [7.9, 27.0] than APN 8.7% [4.4, 13.2] with $p=0.044$, which was not expected because APX and APN were identical algorithms overnight. During the period immediately after exercise and before lunch, participants during APX again had higher percent time in hyperglycemia of 13.1% [0.0, 56.3] compared with APN of 7.7% [0.0, 54.2], but this was not significant ($p=0.2959$). Between lunch and the end of the study, participants during APX also had higher percent time in hyperglycemia, 49.6% [0.0, 94.4] compared with APN, 38.6% [0.0, 89.1] and again this was not significant ($p=0.1437$).

The sharp drop in glucose during exercise occurred during the SAP as well as the APX and APN trials. During the SAP condition, many participants avoided hypoglycemia post-exercise because they anticipated the exercise and adjusted their basal and pre-meal insulin in advance of exercise. A total of 90% of participants reduced their basal insulin bolus during the SAP trial in anticipation of the exercise event and 33% adjusted their pre-breakfast bolus. In SAP, participants had their lowest insulin-on-board (IOB) at the start of exercise, at a mean of 8.9% of total daily insulin requirement (TDIR) versus 13.4% and 15.7% for APN and APX, respectively ($p<0.001$). This is shown in Figure 4 which plots the actual insulin infusion rate (IIR) minus the participants' standard IIR based on their baseline pump profile during the SAP trial for all participants (gray) and the average (black). Notice that prior to and during exercise, nearly all participants reduced their basal insulin in anticipation of the exercise event.

There were no differences in any measures observed based on gender. There were no differences in the total amount of insulin given across the three arms of the study. As expected, there was more glucagon given during the APX arm compared with the APN arm, especially in the time period immediately after the start of exercise and prior to lunch. However, over the course of the entire experiment, there was not a statistically significant difference in the amount of glucagon given in APX compared with APN.

There were 11 adverse events during the study, including 5 instances of nausea: 2, 2, and 1 for APN, APX, and SAP, respectively. There was 1 episode of mild edema at the site of glucagon infusion during an APN study. One participant experienced chills and lightheadedness after an APN study. One participant developed a rash between study visits, which was determined to be unrelated to the study. There were no instances of failed sensors in this data set and no problems with missing sensor data. Five glucagon cartridges suffered from occlusion problems. Of these, four could be fixed and one had to be changed. Two insulin cartridges failed and had to be changed.

Discussion

Results from this study indicate the importance of incorporating exercise detection and adjusted dosing in response to exercise within the context of a dual-hormonal AP. An AP that adjusts dosing in response to exercise can reduce hypoglycemia primarily post-exercise

compared with an AP that does not adjust dosing in response to exercise. Hypoglycemia occurred primarily after the exercise event, which was expected for two reasons; (1) the kinetics and dynamics of insulin and glucagon sensitivity limit their effect on the body during a 45 minute exercise event and (2) increased insulin sensitivity is affected up to 11 hours after an exercise event has occurred (22). While Figure 2 shows that APX led to higher glucose levels compared with APN between the start of exercise and the lunch event for some subjects, the effect was not statistically significant ($p=0.2959$) and there was also not a statistically significant difference after lunch ($p=0.1437$). While not statistically significant, the higher time in hyperglycemia during APX compared with APN after exercise is what we would expect because dosing more glucagon and less insulin during and immediately after exercise has the potential to increase time spent in hyperglycemia. In the future, we plan to incorporate an adaptive element into the dosing so that if a participant experiences hyperglycemia during or after the exercise event, the exercise dosing algorithm will be less aggressive on subsequent exercise events. During the overnight period, participants in APX spent more time in hyperglycemia compared with APN ($p=0.044$), which we expect is a result of a type 1 error since there was no difference between the APX and APN control algorithms overnight.

Participants in this study were adept at adjusting insulin for exercise during SAP, resulting in time in euglycemia of 71.6% of the study during SAP control, but this was at the expense of having more hyperglycemia compared with the APN arm of the study. Remarkably, the high percent of time in euglycemia for the SAP arm is comparable with performance of many AP systems including our prior results (2, 6, 16). While use of the AP yielded a higher percentage time in euglycemia (81.4% for APN and 74.6% for APX), it is clear that participants in this study were very actively managing their glucose levels during SAP therapy and specifically anticipating the forthcoming exercise event. This is particularly apparent in Figure 4 which shows how during SAP, nearly all participants (90%) reduced their basal insulin prior to exercise and 44% reduced their pre-breakfast bolus in anticipation of the exercise. While this caused some hyperglycemia leading up to the exercise event, it helped participants avoid exercise-induced hypoglycemia during the SAP arm of the study. Because this was an in-hospital study, participants had the time to pay close attention to their glucose levels and dosing, and importantly, they knew that they would be exercising 2 hours after breakfast. The AP had no prior knowledge of the exercise event. Without this prior knowledge, the AP could not adjust pre-meal boluses and basal insulin levels prior to the exercise, making it challenging for the control algorithm to appropriately respond to exercise and avoid hypoglycemia. Despite this lack of use of prior knowledge, the participants in the APX group had the lowest percent time in hyperglycemia and the fewest marked hypoglycemia events compared with APN and SAP. SAP also required overall significantly more rescue carbohydrates throughout the entire study duration than APX or APN, making AP usage an attractive option for people with type 1 diabetes wishing to reduce excess carbohydrate intake.

The results presented here are the first to show in a randomized controlled crossover trial how adjusting insulin and glucagon in response to exercise can reduce hypoglycemia compared with an AP that does not adjust dosing. Other studies done on the topic of dosing adjustment in an AP in response to exercise have been inconclusive with regards to

hypoglycemia prevention. A study by Sherr et al. showed that the use of an insulin-only AP during an inpatient stay that included exercise could reduce nocturnal hypoglycemia, but did not reduce daytime hypoglycemia or hypoglycemia during exercise. The study by Turksoy et al. (23) detected exercise and adjusted dosing using an insulin-only AP. They found that use of the AP could reduce hypoglycemia compared with pump therapy, and that when an exercise adjustment algorithm was used (16), hypoglycemia was eliminated entirely. However the sample size of participants using the exercise-adjusted AP was very small and the difference in hypoglycemia between the AP and the exercise-adjusted AP was not significant. Only three out of nine participants doing the AP study used the exercise-adjusted algorithm. Participants using the exercise-adjusted AP all consumed carbohydrates during exercise when their glucose levels were predicted to go low thus helping them avoid hypoglycemia. Consumption of carbohydrates prior to or during exercise was also a confounding issue in a bi-hormonal AP study by Haidar et al.(16). Breton et al. (15) performed a randomized crossover trial that looked at whether elevated heart rate (125% of resting heart rate) could inform a control algorithm by reducing the amount of insulin delivered during exercise within a control-to-range AP. While they found that the rate of glucose decline could be reduced when including heart rate, they did not find a statistically significant reduction in hypoglycemia. The reason that their study did not reach significance for preventing hypoglycemia could have been because of the smaller number of participants (12) but it could have also been because glucagon was not used within their single-hormone AP system as it was in the current study.

There are several limitations of this study. First, the study was done entirely in the hospital. While participants were free to move about the hospital, they may not have behaved as they would have at home or work. This in-hospital artificial test environment during which participants had a lot of time to manage their glucose is likely the reason why participants had such good control during the SAP arm of the study. Another limitation is the absence of a single hormone AP arm. Because of this, it is not known whether it was the reduced insulin or the increased glucagon given during APX that prevented the hypoglycemia. Future studies will include another arm of the study to compare single-hormone with dual-hormone. Because insulin has such a long action time compared with glucagon, we expect that the glucagon will be important in helping prevent exercise-induced hypoglycemia. Future work will investigate the advantage that dual-hormonal AP provides during and after exercise events that do not require carbohydrate consumption. Another limitation of the study was that only aerobic exercise was considered in this study. Work by Yardley et al.(24) has shown that resistance exercise does not yield the same steep drops in glucose that has been shown in people with type 1 diabetes in response to aerobic exercise. Accurately detecting aerobic vs. anaerobic exercise may be necessary when considering how to adjust dosing appropriately in an AP. Other future considerations should include assessing the impact of varying durations and intensities of exercise and the impact of the exercise environment (e.g. training vs. competition). An additional limitation is that this study was originally powered to detect the difference between APX versus SAP, but not APX versus APN. Despite this limitation, we observed a difference between APX and APN as described. Lastly, in this study, during the APX arm, exercise was announced to the AP through a button on the phone. In practice, this is a burden on the participants that may not be used in practice. In the

future, we will automate the detection of exercise by estimating energy expenditure using body-worn accelerometer and heart rate sensors along with a detection algorithm described previously (21).

Conclusions

Exercise can be managed effectively during an in-hospital trial by a dual-hormone AP system with an exercise adjustment algorithm or with sensor-augmented pump therapy if insulin is adjusted well in advance of exercise.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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PGJ, JC, and JEY contributed to the writing, literature search, study design, data collection, data analysis, data interpretation, AP system construction and figures. RR, NR, NP, JC, and JL contributed to the data analysis, data collection, AP system construction, and figures. KK, DB, MJ, CE, and UR contributed to the data collection and tables. KR contributed to the statistical analysis and tables. Dr. Jacobs and Dr. Castle have a financial interest in Pacific Diabetes Technologies Inc., a company that may have a commercial interest in the results of this research and technology.

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References

1. Prevention. CfDCA. U.S. Department of Health and Human Services CfDCA. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States. Atlanta, GA: 2011.
2. Thabit H, Tauschmann M, Allen JM, Leelarathna L, Hartnell S, Wilinska ME, et al. Home Use of an Artificial Beta Cell in Type 1 Diabetes. *The New England journal of medicine*. 2015; 373(22):2129–40. [PubMed: 26379095]
3. Kropff J, Del Favero S, Place J, Toffanin C, Visentin R, Monaro M, et al. 2 month evening and night closed-loop glucose control in patients with type 1 diabetes under free-living conditions: a randomised crossover trial. *The lancet Diabetes & endocrinology*. 2015; 3(12):939–47. [PubMed: 26432775]
4. Jacobs PG, El Youssef J, Castle J, Bakhtiani P, Branigan D, Breen M, et al. Automated control of an adaptive bihormonal, dual-sensor artificial pancreas and evaluation during inpatient studies. *IEEE transactions on bio-medical engineering*. 2014; 61(10):2569–81. [PubMed: 24835122]
5. Castle JR, Engle JM, El Youssef J, Massoud RG, Yuen KC, Kagan R, et al. Novel use of glucagon in a closed-loop system for prevention of hypoglycemia in type 1 diabetes. *Diabetes care*. 2010; 33(6):1282–7. [PubMed: 20332355]
6. Russell SJ, El-Khatib FH, Sinha M, Magyar KL, McKeon K, Goergen LG, et al. Outpatient glycemic control with a bionic pancreas in type 1 diabetes. *The New England journal of medicine*. 2014; 371(4):313–25. [PubMed: 24931572]

7. Tsintzas, K.; MacDonald, IA. Type 1 Diabetes: Clinical Management of the Athlete. London, Dordrecht, Heidelberg, New York: Springer; 2012.
8. Basu R, Johnson ML, Kudva YC, Basu A. Exercise, hypoglycemia, and type 1 diabetes. *Diabetes technology & therapeutics*. 2014; 16(6):331–7. [PubMed: 24811269]
9. Tansey MJ, Tsalikian E, Beck RW, Mauras N, Buckingham BA, Weinzimer SA, et al. The effects of aerobic exercise on glucose and counterregulatory hormone concentrations in children with type 1 diabetes. *Diabetes care*. 2006; 29(1):20–5. [PubMed: 16373890]
10. Tsalikian E, Kollman C, Tamborlane WB, Beck RW, Fiallo-Scharer R, et al. Diabetes Research in Children Network Study G. Prevention of hypoglycemia during exercise in children with type 1 diabetes by suspending basal insulin. *Diabetes care*. 2006; 29(10):2200–4. [PubMed: 17003293]
11. Schiavon M, Dalla Man C, Kudva YC, Basu A, Cobelli C. In silico optimization of basal insulin infusion rate during exercise: implication for artificial pancreas. *Journal of diabetes science and technology*. 2013; 7(6):1461–9. [PubMed: 24351172]
12. Tanenberg RJ, Newton CA, Drake AJ. Confirmation of hypoglycemia in the "dead-in-bed" syndrome, as captured by a retrospective continuous glucose monitoring system. *Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists*. 2010; 16(2):244–8.
13. Cryer PE. Mechanisms of hypoglycemia-associated autonomic failure in diabetes. *The New England journal of medicine*. 2013; 369(4):362–72. [PubMed: 23883381]
14. McMahon SK, Ferreira LD, Ratnam N, Davey RJ, Youngs LM, Davis EA, et al. Glucose requirements to maintain euglycemia after moderate-intensity afternoon exercise in adolescents with type 1 diabetes are increased in a biphasic manner. *The Journal of clinical endocrinology and metabolism*. 2007; 92(3):963–8. [PubMed: 17118993]
15. Breton MD, Brown SA, Karvetski CH, Kollar L, Topchyan KA, Anderson SM, et al. Adding heart rate signal to a control-to-range artificial pancreas system improves the protection against hypoglycemia during exercise in type 1 diabetes. *Diabetes technology & therapeutics*. 2014; 16(8):506–11. [PubMed: 24702135]
16. Haidar A, Legault L, Messier V, Mitre TM, Leroux C, Rabasa-Lhoret R. Comparison of dual-hormone artificial pancreas, single-hormone artificial pancreas, and conventional insulin pump therapy for glycaemic control in patients with type 1 diabetes: an open-label randomised controlled crossover trial. *The lancet Diabetes & endocrinology*. 2015; 3(1):17–26. [PubMed: 25434967]
17. Sherr JL, Cengiz E, Palerm CC, Clark B, Kurtz N, Roy A, et al. Reduced hypoglycemia and increased time in target using closed-loop insulin delivery during nights with or without antecedent afternoon exercise in type 1 diabetes. *Diabetes care*. 2013; 36(10):2909–14. [PubMed: 23757427]
18. Stenerson M, Cameron F, Payne SR, Payne SL, Ly TT, Wilson DM, et al. The impact of accelerometer use in exercise-associated hypoglycemia prevention in type 1 diabetes. *Journal of diabetes science and technology*. 2015; 9(1):80–5. [PubMed: 25231116]
19. Turksoy K, Bayrak ES, Quinn L, Littlejohn E, Cinar A. Multivariable adaptive closed-loop control of an artificial pancreas without meal and activity announcement. *Diabetes technology & therapeutics*. 2013; 15(5):386–400. [PubMed: 23544672]
20. Pescatello, LS. American College of Sports Medicine Guidelines for Exercise Testing and Prescription. 9. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins Health; 2014.
21. Jacobs PG, Resalat N, El Youssef J, Reddy R, Branigan D, Preiser N, et al. Incorporating an Exercise Detection, Grading, and Hormone Dosing Algorithm Into the Artificial Pancreas Using Accelerometry and Heart Rate. *Journal of diabetes science and technology*. 2015; 9(6):1175–84. [PubMed: 26438720]
22. Davey RJ, Howe W, Paramalingam N, Ferreira LD, Davis EA, Fournier PA, et al. The effect of midday moderate-intensity exercise on postexercise hypoglycemia risk in individuals with type 1 diabetes. *The Journal of clinical endocrinology and metabolism*. 2013; 98(7):2908–14. [PubMed: 23780373]
23. Turksoy K, Quinn LT, Littlejohn E, Cinar A. An integrated multivariable artificial pancreas control system. *Journal of diabetes science and technology*. 2014; 8(3):498–507. [PubMed: 24876613]

24. Yardley JE, Kenny GP, Perkins BA, Riddell MC, Balaa N, Malcolm J, et al. Resistance versus aerobic exercise: acute effects on glycemia in type 1 diabetes. *Diabetes care*. 2013; 36(3):537–42. [PubMed: 23172972]

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Figure 1.
Trial profile.

Figure 2.

(a) Glucose from the start of exercise to the end of the study. The 25% and 75% interquartile ranges are shown for both APN and APX trials as well as the upper and lower 95%. Notice that while APN and APX yielded similar results during the exercise period (glucose dropped sharply), participants generally had lower glucose under the APN trial for the 2 hours post exercise compared with the APX trial. Also shown are (b) insulin, (c) glucagon, and (d) rescue carbohydrates.

Figure 3.

Control variability plots for (a) SAP, (b) APN, and (c) APX arms for the entire study duration excluding the first 4 hours of run-in. Notice that for the SAP trial, participants experienced more hyperglycemia and also a significant number of hypoglycemia events.

Figure 4.

Actual IIR minus expected IIR during the SAP trial for all participants (gray traces) and the mean (black). Prior to exercise, nearly all participants reduced their basal insulin.

Statistical results from the study

Table 1

	Dual-hormone AP with dosing adjustment during exercise (APX) (n=21)	Dual-hormone AP with no dosing adjustment during exercise (APN) (n=21)	Sensor-augmented pump (SAP)therapy (n=21)	APX minus APN, p value	APX minus SAP, p value	APN minus SAP, p value
From exercise (primary outcomes)						
% time <3.9 mmol/L *	0.3% [-0.1, 0.7]	3.1% [0.8, 5.3]	0.8% [0.1, 1.4]	-2.8% [-5.0, -0.5] 0.001	-0.5% [-1.2, 0.2] 0.16	2.3% [-0.1, 4.7] 0.024
% time 3.9–10 mmol/L *	67% [60, 75]	72% [66, 78]	68% [60, 76]	-5% [-15, 5] 0.33	-0% [-1.1, 1.1] 0.95	5% [-5, 14] 0.35
(secondary outcome) % time >10 mmol/L *	32% [25, 39]	25% [19, 30]	31% [24, 39]	7% [-1, 16] 0.09	1% [-10, 12] 0.92	-7% [-15, 2] 0.11
From study start (secondary outcomes)						
% time <3.9 mmol/L	0.2% [-0.1, 0.4]	1.7% [0.6, 2.8]	1.5% [0.6, 2.4]	-1.5% [-2.7, -0.4] 0.006	-1.3% [-2.3, -0.4] 0.007	0.2% [-1.4, 1.8] 0.82
% time 3.9–10 mmol/L	75% [68, 81]	81% [78, 85]	72% [64, 79]	-6% [-14, 1] 0.11	3% [-6, 12] 0.50	9% [1, 18] 0.044
% time >10 mmol/L	25% [19, 32]	17% [14, 21]	27% [19, 34]	8% [1, 15] 0.023	-2% [-11, 7] 0.72	-10% [-18, -1] 0.013
Events CBG <3.9 mmol/L [count, mean]	5.024 [0.01, 0.47]	7.033 [0.10, 0.56]	9.043 [0.14, 0.72]	-0.09 [-0.40, 0.22] 0.59	-0.19 [-0.57, 0.18] 0.33	-0.10 [-0.40, 0.19] 0.49
Events CBG <2.8 mmol/L [†] [count]	1	0	1			
Number of rescue carb treatments [count, mean]	6.030 [-0.01, 0.61]	9.041 [0.09, 0.73]	7.033 [-0.03, 0.70]	-0.11 [-0.54, 0.32] 0.62	-0.04 [-0.42, 0.35] 0.85	0.08 [-0.21, 0.37] 0.63
Mean CBGs taken	9.5 [8.8, 10.2]	10.2 [9.4, 11.0]	9.8 [8.4, 11.1]	-0.7 [-1.8, 0.4] 0.23	-0.2 [-1.5, 1.0] 0.70	0.4 [-1.3, 2.2] 0.61
Insulin delivery [U/kg]	0.40 [0.36, 0.45]	0.38 [0.34, 0.42]	0.37 [0.33, 0.41]	0.03 [-0.01, 0.06] 0.17	0.03 [0.00, 0.06] 0.026	0.01 [-0.02, 0.03] 0.66
Glucagon delivery [mcg/kg]	3.6 [2.6, 4.6]	2.8 [2.2, 3.4]	n/a	0.8 [-0.0, 1.7] 0.06	n/a	n/a
Mean glucose [mmol/L]	8.6 [8.1, 9.1]	8.1 [7.8, 8.3]	8.6 [7.9, 9.2]	0.5 [0.0, 1.1] 0.032	0.0 [-0.6, 0.7] 0.90	-0.5 [-1.2, 0.1] 0.13
Standard deviation of glucose [mmol/L]	2.3 [2.0, 2.6]	2.2 [1.9, 2.5]	2.7 [2.3, 3.0]	0.1 [-0.3, 0.5] 0.65	-0.3 [-0.8, 0.1] 0.13	-0.4 [-0.9, 0.0] 0.07
Glucose at start of exercise [mmol/L]	9.3 [8.3, 10.3]	8.6 [7.7, 9.5]	9.0 [7.9, 10.0]	0.7 [-0.1, 1.5] 0.10	0.3 [-1.1, 1.7] 0.66	-0.4 [-1.7, 0.9] 0.58
Glucose at end of exercise [mmol/L]	6.4 [5.4, 7.4]	5.9 [5.2, 6.6]	7.1 [6.2, 8.0]	0.5 [-0.5, 1.5] 0.34	-0.7 [-2.1, 0.6] 0.28	-1.2 [-2.4, -0.0] 0.049

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Data are mean (95% CI) unless otherwise indicated.
* A p value of less than 0.0167 was regarded as significant.
‡ Too few events to estimate mean and 95% CI.

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