ORIGINAL ARTICLE

Mitigating Reductions in Glucose During Exercise on Closed-Loop Insulin Delivery: The Ex-Snacks Study

Neha S. Patel, DO, Michelle A. Van Name, MD, Eda Cengiz, MD, MHS, Lori R. Carria, MS, Eileen M. Tichy, MMSc, PA-C, RD, Kate Weyman, APRN, Stuart A. Weinzimer, MD, William V. Tamborlane, MD, and Jennifer L. Sherr, MD, PhD

Abstract

Objective: To assess whether snacking could be used with closed-loop (CL) insulin delivery to avoid exercise-induced reductions in plasma glucose (PG), as well as elevations in PG at the end of exercise.

Research Design and Methods: Twelve type 1 diabetes (T1D) subjects (age 13–36 years, duration 10.7 ± 8.4 years, A1c $7.4\% \pm 0.8\%$ [57 ± 8.7 mmol/mol]) underwent two 105-min exercise studies while under CL control: CL alone and CL+snack. Exercise, commenced at 3 PM, consisted of four 15-min periods of brisk treadmill walking to 65%–70% HR_{max} (separated by three 5-min rest periods), followed by a 30-min recovery period. Fifteen to 30 g carbohydrate (Gatorade) was provided on snacking visits just before and midway through the exercise period. PG and insulin were measured every 15–20 min during the exercise studies.

Results: Baseline PG levels were similar for CL alone (164 ± 16 mg/dL) versus CL+snack (172 ± 11 mg/dL). During exercise, PG levels fell by 53 ± 10 mg/dL without snacking versus a modest 10 ± 13 mg/dL increase in PG with snacking ($P=0.0005$); similar differences in the change in PG levels were observed at the end of recovery period. Hypoglycemia requiring rescue treatment (PG ≤ 60 mg/dL) during exercise occurred in three nonsnacking visits versus none with snacking. During the 75-min exercise period, insulin delivered was 1.8 ± 0.4 U for the CL+snack admission compared to 0.7 ± 0.1 U during CL alone ($P=0.002$).

Conclusion: These results support the use of a simple snacking strategy to avoid exercise-induced lowering of PG while on CL insulin delivery. Persistent insulin infusion during exercise with snacking also appears to be effective in limiting increases in PG at the end of exercise.

Keywords: Closed-loop systems, Artificial pancreas, Type 1 diabetes, Pediatrics, Carbohydrate counting.

Introduction

WHILE REGULAR EXERCISE is an important component of treatment of type 1 diabetes (T1D) to enhance cardiovascular health, limit excessive weight gain, and improve self-image, it remains a double-edged sword for many patients. Efforts to avoid hypoglycemia by snacking with or without suspending basal insulin delivery in pump-treated patients are often either unsuccessful or result in hyperglycemia during or immediately after exercise. In addition, individuals with T1D are at greater risk for hypoglycemia on

nights following antecedent afternoon exercise¹ due, in part, to blunted epinephrine responses to hypoglycemia during sleep.^{2,3}

McMahon et al. have reported that the risk of nocturnal hypoglycemia is greatest 7–11 h following midafternoon exercise due to a transient increase in insulin sensitivity.⁴ We have recently demonstrated that closed-loop (CL) insulin delivery can markedly reduce the risk of nocturnal hypoglycemia by automatically lowering the basal insulin infusion during this period of excess risk.⁵ However, CL control failed to prevent hypoglycemia during exercise in that study.

Yale School of Medicine, Yale Pediatric Endocrinology & Diabetes, New Haven, Connecticut.

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Dual-hormone CL systems incorporating insulin and glucagon may provide a means to prevent exercise-induced hypoglycemia, but the requirement for separate infusions of insulin and glucagon increases the costs and complexity of such devices.^{6,7} It has also been suggested that adding activity monitors to artificial pancreas systems may protect against exercise-induced hypoglycemia by alerting the system to reduce insulin delivery even before sensor glucose levels begin to fall.^{8,9} However, the Diabetes Research in Children Network (DirecNet) Study Group has showed that disconnecting an insulin pump before the start of exercise often fails to prevent exercise-induced hypoglycemia due to persistence of insulin action even after suspending basal insulin delivery.¹⁰ The Ex-Snacks study was consequently undertaken to test the hypothesis that a proactive snacking strategy in combination with CL insulin delivery would provide a simple and effective means to decrease exercise-induced reductions in plasma glucose (PG), as well as limit increases in PG with snacking at the end of exercise, in individuals with T1D.

Research Designs and Methods

Subjects were recruited from the Yale Type 1 Diabetes Program and through local advertising. Inclusion criteria included age 13–45 years, clinical diagnosis of T1D of at least 1-year duration, current use of insulin pump therapy for at least 3 months, A1c <9% (<75 mmol/mol), body weight >40 kg to accommodate phlebotomy, ability to complete the 75-min exercise protocol, normal hematocrit, no other chronic medical condition that would interfere with safety of study, and no medications (other than insulin) known to affect blood glucose levels or heart rate; female subjects should not be pregnant or lactating. After a complete explanation of the study protocol, written informed consent was obtained in subjects ≥18 years; in subjects <18 years, both adolescent assent and parental permission were obtained. The study was approved by the Yale University Human Investigations Committee.

Study Design

The study utilized a randomized, crossover design in which subjects were studied under two conditions: CL alone and CL+snack. The difference in the change in PG levels from baseline to the end of exercise under the two-study conditions was the primary outcome measure.

Study Procedures

Preparation for exercise studies

At enrollment, the subject's home insulin pump was replaced with a Medtronic Revel study pump and an Enlite 2 sensor was placed 3–4 days before each exercise study. All subjects arrived at the Yale Outpatient Clinical Research Center fasting between 7 and 8 AM on the morning of the exercise studies, at which time an intravenous catheter was inserted for blood sampling. Pump data from the prior 72 h were used to determine algorithm parameters and hybrid CL control was initiated. On both study days, identical, self-selected breakfast and lunch meals were provided at 8:00 AM and 12:00 PM. Carbohydrate intake for breakfast averaged 41 ± 7 (range 13–54) grams and lunch 69 ± 8 (range 27–107)

grams. Insulin to carbohydrate ratios were determined based on algorithm calculations and were verified by study staff to be similar to usual outpatient insulin to carbohydrate ratios utilized. No snacks were allowed, except for treatment of hypoglycemia, or per protocol for the exercise snacking admission.

System considerations

The hybrid CL system used in this study consisted of four components: a Medtronic Revel 2.0 insulin pump, a subcutaneous Enlite 2 glucose sensor, the Medtronic Minimed Translator, and an Android mobile device. The Translator converts radiofrequency signals from the pump and sensor to Bluetooth, allowing these devices to communicate with the Android mobile device that houses the proportional–integral–derivative with insulin feedback (PID-IFB) control algorithm.¹¹ The PID-IFB algorithm on the Android phone receives sensor data and calculates insulin doses, which it commands the pump to deliver every 5 min. The algorithm's target PG was set to 150 mg/dL (8.3 mmol/mol) for the duration of CL study during both admissions. This target was specifically chosen to minimize the need for rescue carbohydrate administration for PG <60 mg/dL before the start of exercise during both closed-loop admissions.

Exercise protocol

The exercise protocol utilized in this study was identical to that previously described in the DirecNet studies and our previous CL exercise study.^{1,5,10} Briefly, exercise sessions were scheduled to commence at 3 PM. The exercise session included four 15-min periods of brisk walking on the treadmill, followed by three 5-min rest breaks. The target heart rate was calculated to ~50%–55% maximal effort (equivalent to 65%–70% maximum heart rate), where maximum heart rate was calculated as $220 - \text{subject's age (in years)}$.⁵ Baseline samples were obtained for measurement of PG and insulin before the start of exercise, at the end of each 15-min exercise period, and 15 and 30 min after exercise. If PG was <80 mg/dL, frequency of testing was increased to every 5 min. If PG was ≤60 mg/dL (3.3 mmol/L), the exercise session was stopped and rescue treatment was provided.

CL control±snacking

During the snacking studies, supplemental carbohydrate was provided before and midway through exercise. At both time points, if PG was <150 mg/dL (8.3 mmol/L), 30 g of carbohydrate was provided and if PG was ≥150 mg/dL, 15 g of carbohydrate was provided. The carbohydrate that was provided was Gatorade Prime 01, in which 2 ounces contains 15 g of carbohydrate.

Analytical methods

Plasma insulin levels were measured by radioimmunoassay, PG levels were measured by YSI 2300 Glucose Analyzer (YSI Life Sciences, Yellow Springs, OH), and A1c by the DCA Vantage (Siemens Medical Solutions Diagnostics).

Statistical methods

PG concentrations were used to compare differences in glucose control between the two treatment conditions: CL

TABLE 1. PLASMA GLUCOSE AND INSULIN LEVELS DURING EXERCISE SESSIONS WHILE ON CL

During exercise	CL alone	CL+snack	P
Plasma glucose (mg/dL)			
Start of exercise	164 ± 16	172 ± 11	0.75
End of exercise	111 ± 16	182 ± 9	0.004
Change in plasma glucose during exercise	-53 ± 10	10 ± 13	0.0005
Plasma insulin (μU/mL)			
Start of exercise	69 ± 16	59 ± 12	0.38
End of exercise	59 ± 13	61 ± 13	0.85
Change in plasma insulin during exercise	-10 ± 5	2 ± 4	0.11

P-values represent significance of differences between the study conditions.

CL, closed-loop.

alone versus CL+snack. Hypoglycemia was defined as a PG level ≤60 mg/dL. In the 3 exercise studies that were prematurely terminated due to hypoglycemia, the last PG level before rescue therapy was carried forward. Statistical comparisons between CL-alone and CL+snack conditions were accomplished with paired *t*-tests for normally distributed data and Wilcoxon matched-pairs signed-rank tests for non-normally distributed data. Data are presented as mean ± SE. Calculations were performed using GraphPad Prism 6 (GraphPad Software, San Diego, CA).

Results

Fifteen subjects were recruited into the study. However, one subject withdrew due to problems with insertion of an intravenous catheter and two subjects due to missing school/work. The 12 subjects (six females) who completed the study were aged 20 ± 6 years (range 13–36 years), had diabetes duration of 10.7 ± 8.4 years, BMI of 25.6 ± 4.5 kg/m², and a mean A1c level of 7.4% ± 0.8% (57.0 ± 8.7 mmol/mol).

During the CL+snack studies, 75% of participants received 15 g of carbohydrates as their pre-exercise PG was >150 mg/dL and four subjects received 30 g of carbohydrates as PG

levels were <150 mg/dL. All participants were >150 mg/dL midway through exercise; thus, 15 g of carbohydrates was administered at that juncture.

Baseline PG levels were similar at the start of the exercise protocol for both the CL-alone (164 ± 16 mg/dL) and CL+snack conditions (172 ± 11 mg/dL, *P*=0.75) (Table 1). As shown in Figure 1a and Table 1, mean PG levels fell by 53 ± 10 mg/dL with exercise during CL alone (*P*=0.0015). In contrast, there was a nonsignificant increase in mean PG during the CL+snack condition (10 ± 13 mg/dL, *P*=0.60). The 63 ± 10 mg/dL difference in change of PG levels from baseline to the end of exercise in the two studies was statistically significant (*P*=0.0005) (Table 1). At the end of recovery period (30 min after exercise), the difference in PG was 132 ± 16 mg/dL for CL alone and 183 ± 14 mg/dL for CL+snack (*P*=0.0078). All but one participant in the CL-alone condition had a drop in PG during the course of exercise, while relatively stable glucose levels were noted during the snacking visit (Fig. 2). Hypoglycemia, defined as BG <60 mg/dL, occurred in three nonsnacking visits, whereas no hypoglycemia occurred during snacking sessions (*P*=0.22).

As shown in Figure 1b and Table 1, the fall in PG levels during exercise with CL alone was accompanied by a decline in plasma insulin concentrations from 69 ± 6 μU/mL at baseline to 59 ± 13 μU/mL at the end of exercise (*P*=0.02). In contrast, plasma insulin concentrations did not change significantly during exercise in the CL+snack condition (baseline 59 ± 12 μU/mL vs. end 61 ± 13 μU/mL). Overall, insulin delivery during the 75-min exercise period averaged 0.7 ± 0.1 U in the CL-alone condition versus 1.8 ± 0.4 U in the CL+snack condition (*P*=0.002).

Conclusions

The results presented herein demonstrate that a simple snacking intervention in combination with CL insulin delivery can prevent the fall in PG levels during exercise observed with CL treatment alone. These findings complement our prior work showing that reduction of CL insulin delivery in response to exercise-induced decrements in PG does not prevent marked reductions in PG, due to the gradual fall in

FIG. 1. Changes in plasma glucose and insulin during and immediately after exercise. Changes in plasma glucose (a) and plasma insulin (b) during exercise are shown by the shaded area and for 30 min following exercise. CL-alone condition is depicted as dotted line with circles, and CL+snack condition as solid line with squares. *P*-values indicate change in glucose and insulin levels over time for the 75-min exercise period (shaded region). CL, closed-loop.

FIG. 2. Plasma glucose levels before and at the end of exercise sessions in individual subjects. Each participant is represented by a single line indicating change in glucose level from the start to the end of the exercise period. The dashed line represents the threshold to define hypoglycemia (60 mg/dL).

plasma insulin levels even after basal insulin infusions are being shut down.⁵ These results were observed even without the opportunity to titrate the carbohydrate dose to the needs of individual subjects during exercise.

It is also noteworthy that three subjects in the CL-alone condition required rescue treatment due to a fall in PG levels below 60 mg/dL, compared to no subjects in the CL+snack condition. Hypoglycemic rescue was required in these subjects despite the conscious choice of a conservative system set point to a target of 150 mg/dL to more fully assess the magnitude of the exercise-induced fall in PG during both exercise studies. Indeed, all algorithm parameters were purposefully set to be consistent between the two study conditions. As seen in our subjects with lower baseline PG levels in the CL-alone studies, even suspending the basal insulin infusion completely before the start of exercise did not prevent hypoglycemia in four of the five subjects who had baseline PG levels <130 mg/dL in the DirecNet open-loop pump study.¹¹

A common strategy in preventing hypoglycemia with exercise during open-loop pump therapy is to snack, as well as to reduce or suspend the basal insulin infusion in pump-treated patients. A recent survey to assess strategies for exercise preparation in those with T1D highlighted this, as nearly 80% of respondents endorsed consuming carbohydrates before exercise.¹² Unfortunately, this approach often either fails to prevent hypoglycemia or results in hyperglycemia during or after exercise.¹² In our study, subjects in the CL+snack condition received more than twice as much exogenous insulin during the exercise than subjects in the CL-alone condition. Maintaining plasma insulin levels at or near baseline concentrations helps to explain why hyperglycemia was not observed in the snacking visit during or immediately after exercise. Indeed, on the CL+snack visit, the PG was steady at the end of exercise and 30 min later following cessation of exercise (postexercise PG: 182 ± 9 mg/dL vs. end of recovery period PG: 183 ± 14 mg/dL, $P = 0.71$). Importantly, the amount of insulin infused on the CL+snack visit closely matched usual basal insulin delivery for our participants based on their usual open-loop (OL) pump settings (OL basal: 1.65 ± 0.55 U of insulin vs. CL+snack: 1.8 ± 0.4 U).

Before initiation of the study, consideration was given as to what "dose" of carbohydrate would be administered during the snacking study. An elegant study performed by Riddell and Milliken conducted at a diabetes camp assessed the use of a simple snacking strategy before exercise based on sensor glucose readings.¹³ In that study, when glucose was <90 mg/dL before exercise, consumption of 16 g of carbohydrates failed to prevent hypoglycemia in nearly 40% of cases.¹³ In addition, it has been suggested that those living with type 1 may benefit from consumption of 1–1.5 g of carbohydrate/kg body weight/hour of activity, especially if the activity is occurring during peak insulin action.¹⁴ Therefore, in constructing the present study, we attempted to define a simple strategy carbohydrate "dose" based on glucose level. Instead of providing the entire dose of carbohydrate at the start of the exercise period, the decision was made to split the dose of carbohydrate before and midway through exercise. With this approach, participants consumed, on average, 0.5 g of carbohydrate/kg body weight/hour of activity.

Concern may exist that proactive snacking could lead to excessive weight gain, thus mitigating the beneficial effects of weight loss/maintenance that may be accomplished through regular physical activity. Indeed, the Dose Adjustment for Normal Eating (DAFNE) program in the United Kingdom has highlighted that oftentimes episodes of hypoglycemia may be over treated by those with T1D in clinical practice.¹⁵ Leroux et al. conducted a literature review to explore lifestyle and risk of cardiometabolic risk factors in adults with T1D.¹⁶ While interventional studies demonstrated the clear benefits of physical activity on at least one cardiometabolic risk factor, it was noted that sedentary habits are more prevalent in those with T1D, possibly due to the fear of exercise-induced hypoglycemia.¹⁶

As in other exercise studies in T1D, a limitation of our study is that the findings primarily apply to the conditions of the study; namely, prolonged aerobic exercise in the mid-afternoon, ~3 h after the last premeal bolus dose of insulin. In addition, there was no OL comparator arm in the present study. However, as CL devices near commercial availability, the present study focused on how best to manage glucose levels during exercise with CL systems, as they will likely

become the gold standard of treatment in the not too distant future. Importantly, in a previous study conducted by our group, we compared OL to CL therapy using the same exercise protocol used here. While we found CL therapy reduced nocturnal hypoglycemia, it failed to prevent hypoglycemia during exercise (five subjects required treatments for PG <60 mg/dL during CL control vs. six subjects during OL control [$P = \text{ns}$]).⁵ With these data showing similar rates of hypoglycemia during exercise whether using OL or CL control, the present study was designed to focus on how to manage glycemia during exercise while using a CL system.

Alternate strategies are likely to be needed to manage glycemia during short bursts of high-intensity exercise, with resistance exercise and when exercise occurs shortly after a premeal bolus dose. Future studies might also assess the effectiveness of snacks that include proteins and fats, as well as simple sugars. “Announcing” exercise by transiently increasing the CL system’s target glucose level may also be effective in preventing exercise-induced hypoglycemia,¹⁷ but our data suggest that this may need to be manually programmed 1–2 h before the commencement of exercise to be effective. This requirement would increase patient burden, as it requires forethought and would preclude the ability to exercise spontaneously. Also, it is possible that if the exercise session is skipped, this strategy could lead to late-onset hyperglycemia due to reductions in insulin delivery secondary to alterations in system targets. Recently, with stable glucagon preparations, the use of minidose glucagon as an alternative to oral carbohydrates has been explored.^{18,19} More complex systems for exercise detection have been developed, which allows for automatic adjustment of algorithm parameters.^{20,21} Yet, commercial availability of such systems is likely to lag behind the first generation of insulin-only, hybrid closed-loop systems; thus, a simple snacking strategy may bridge the time until more complex systems are approved.

As has been demonstrated in other artificial pancreas studies involving adjunctive treatments with pramlintide and liraglutide,²² the results of this study demonstrate that CL system performance can be improved by clinical strategies that do not depend on changes in the controller algorithm or the need to infuse glucagon to prevent hypoglycemia. While the CL system on its own could not decrease the rate of hypoglycemia that occurred during exercise, combining CL control with a simple snacking regimen decreased the magnitude of exercise-induced PG reductions, as well as the risk of hyperglycemia during and immediately after exercise.

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Author Contributions

N.S.P. and J.L.S. researched data and wrote the manuscript. M.A.V., E.C., L.C., K.W., and E.T. researched data and contributed to the discussion. W.V.T. and S.A.W. researched data, contributed to the discussion, and reviewed and edited the manuscript. N.S.P. is the guarantor of this work, and as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

Author Disclosure Statement

Medtronic Diabetes provided the pumps, sensors, infusion sets, reservoirs, and Android phones for the CL experiments. W.V.T. is a consultant for Medtronic Diabetes, NovoNordisk, and Sanofi. S.A.W. is a consultant for Medtronic Diabetes and Tandem, and serves on a Medical Advisory Board for Insulet. E.C. is a speaker for NovoNordisk. No other potential conflicts of interest relevant to this article were reported. No sponsor had any role in the study design, data collection, data analysis, data interpretation, or writing of the report.

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Address correspondence to:

Neha S. Patel, DO

Yale School of Medicine

Yale Pediatric Endocrinology & Diabetes

One Long Wharf Drive Suite 503

New Haven, CT 06510

E-mail: neha.patel@yale.edu