Closed-Loop Basal Insulin Delivery Over 36 Hours in Adolescents With Type 1 Diabetes

Randomized clinical trial

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OBJECTIVE—We evaluated the safety and efficacy of closed-loop basal insulin delivery during sleep and after regular meals and unannounced periods of exercise.

RESEARCH DESIGN AND METHODS—Twelve adolescents with type 1 diabetes (five males; mean age 15.0 [SD 1.4] years; HbA_{1c} 7.9 [0.7]%; BMI 21.4 [2.6] kg/m^2) were studied at a clinical research facility on two occasions and received, in random order, either closed-loop basal insulin delivery or conventional pump therapy for 36 h. During closed-loop insulin delivery, pump basal rates were adjusted every 15 min according to a model predictive control algorithm informed by subcutaneous sensor glucose levels. During control visits, subjects' standard infusion rates were applied. Prandial insulin boluses were given before main meals (50–80 g carbohydrates) but not before snacks (15–30 g carbohydrates). Subjects undertook moderate-intensity exercise, not announced to the algorithm, on a stationary bicycle at a 140 bpm heart rate in the morning (40 min) and afternoon (20 min). Primary outcome was time when plasma glucose was in the target range (71–180 mg/dL).

RESULTS—Closed-loop basal insulin delivery increased percentage time when glucose was in the target range (median 84% [interquartile range 78–88%] vs. 49% [26–79%], $P = 0.02$) and reduced mean plasma glucose levels (128 [19] vs. 165 [55] mg/dL, $P = 0.02$). Plasma glucose levels were in the target range 100% of the time on 17 of 24 nights during closed-loop insulin delivery. Hypoglycemia occurred on 10 occasions during control visits and 9 occasions during closed-loop delivery (5 episodes were exercise related, and 4 occurred within 2.5 h of prandial bolus).

CONCLUSIONS—Day-and-night closed-loop basal insulin delivery can improve glucose control in adolescents. However, unannounced moderate-intensity exercise and excessive prandial boluses pose challenges to hypoglycemia-free closed-loop basal insulin delivery.

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Closed-loop insulin delivery is an emerging technology that may transform management of type 1 diabetes (1). Coupling subcutaneous continuous glucose monitoring (2,3) and insulin pump delivery (4), the closed-loop technology delivers insulin in a continually glucose-responsive fashion to reduce the risk of hypoglycemia and to improve overall glucose control (5,6).

This novel approach differs from conventional pump therapy through the use of a control algorithm that directs subcutaneous insulin delivery according to subcutaneous sensor glucose levels (7). Previous randomized studies with an adaptive algorithm controlling basal insulin demonstrated effectiveness of closed loop during sleep (8,9). Application after a standard evening meal and late-afternoon exercise resulted in a 20% improvement in the number of glucose levels overnight within the target range while reducing the risk of nocturnal hypoglycemia in children and adolescents (8). Similar improvements were observed in adults after a standard dinner and a large evening meal accompanied by alcohol (9). Feasibility of closed-loop control has also been explored in pregnancy (10,11). The future challenge is to determine whether closed-loop insulin delivery can maintain glycemic control after meals, physical exercise, and snacks, where to date, published studies have been encouraging but have lacked a conventional therapy comparator (12,13).

Meals and physical activity cause rapid fluctuations in blood glucose levels, which challenge the closed-loop approach because of delays associated with the subcutaneous route of insulin delivery and glucose sensing errors. We addressed this question by evaluating closed-loop basal insulin delivery systems with proven efficacy overnight during a 36-h period that comprised waking hours and common daily activities, including a typical school day, and behaviors of adolescents.

RESEARCH DESIGN AND METHODS

We carried out an open-label, randomized controlled crossover study to compare closed-loop basal insulin delivery and conventional pump therapy in adolescents with type 1 diabetes. The study aimed to replicate common daily activities during two 36-h study periods, each comprising 2 nights and 1 day.

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The study was approved by the Southampton and South West Hampshire Research Ethics Committee B. Participants <16 years of age provided assent to the study procedures, and informed consent was signed by the parent or caregiver. Subjects ≥16 years of age signed their own consent before participation.

Setting and subjects

The study was conducted at the Wellcome Trust Clinical Research Facility at Addenbrooke's Hospital (Cambridge, U.K.) between March and November 2010. Young people aged 12–18 years from 3 pediatric diabetes clinics at Cambridge University Hospital, London and Norwich, took part. Inclusion criteria were type 1 diabetes (World Health Organization criteria), duration of at least 1 year, and insulin pump therapy for at least 3 months. C-peptide level was not measured. Adolescents with poor glycemic control (HbA_{1c} >12% [108 mmol/mol]) and significant insulin resistance (total daily dose >2 units/kg/day) were excluded. Additional exclusion criteria were clinically significant nephropathy or retinopathy and hypoglycemia unawareness. Subjects used an insulin bolus calculator to titrate prandial insulin boluses. Insulin-to-carbohydrate ratios and insulin sensitivity factors were determined in collaboration with treating clinicians. Supplementary Fig. 1 shows the flow of participants through the study.

Study design

Subjects attended the clinical research facility on two occasions and underwent closed-loop basal insulin delivery and conventional pump therapy in random order. The visits were separated by an interval of 1–6 weeks, during which continuous glucose monitoring was discontinued and subjects continued their standard insulin pump therapy and diet regimen.

Study procedures

Continuous glucose monitoring was established 24–48 h before each study visit by inserting a single subcutaneous glucose sensor (SEVEN PLUS; Dexcom, Inc; San Diego, CA) into the subcutaneous tissue of the abdomen. Calibration followed manufacturer's instructions, which included finger-stick glucose measurements taken every 12 h using the subject's own glucose meter checked for accuracy by calibration fluid.

On each occasion, subjects were admitted at 1730 h on day 1 and stayed until 0800 h on day 3. On arrival, the subject's insulin pump was replaced with a study pump (Animas 2020; Johnson & Johnson, Lititz, PA) connected to the existing infusion site and infusing the rapid-acting insulin analog aspart (Novo Nordisk, Bagsværd, Denmark). An intravenous cannula was inserted into an antecubital vein and kept patent with saline to allow for frequent blood sampling starting at 1830 h on day 1.

Meals and activities

The subjects consumed self-selected meals and snacks from standardized menus that were identical on the two study visits. Meals (breakfast 50 g carbohydrates at 0800 h, lunch 70 g at 1300 h, and dinner 80 g at 1900 h) were accompanied by insulin boluses calculated using the subjects' standard insulin pump bolus calculator settings. Meal boluses included correction according to premeal finger-stick glucose levels. At a finger-stick value of ≤72 mg/dL, boluses were given with the meal; otherwise, they were given 10 min before the meal. Snacks containing 15 g carbohydrates were given in the evening at 2100 h on day 1 and day 2 and in the morning at 1015 h on day 2. An afternoon snack of 30 g carbohydrates was consumed at 1600 h on day 2. No insulin boluses were given before these snacks during either the conventional pump therapy or the closed-loop basal insulin delivery. Subjects were discouraged from taking additional finger-stick measurements between meals. Hypoglycemia was treated with oral carbohydrates (15–30 g in drink), adopting an identical protocol in the two treatment arms.

Subjects engaged in physical activity consisting of two 20-min walks outside the clinical research facility within the hospital campus at 0840 and 1530 h on day 2 and two structured, moderate-intensity exercise sessions on a stationary bicycle at a heart rate of 140 bpm. The latter included a morning session of 40 min duration at 1040 h and a 20-min session in the afternoon at 1730 h. Subjects engaged in other common daily activities, such as playing computer games, reading, and watching television.

Physical activity energy expenditure (PAEE) was evaluated by an Actiheart monitor (CamNtech Ltd, Cambridge, U.K.) measuring combined heart rate and acceleration (14,15) to ensure comparable activity on the two occasions. Subjects were fitted with the Actiheart monitor on arrival. The monitor was calibrated using an 8-min step test (16). After the end of the first study visit, subjects wore the Actiheart monitor for an additional 36–72 h to evaluate PAEE in the home setting between study visits.

Closed-loop basal insulin delivery

An algorithm based on model predictive control (7) was used to alter basal insulin delivery during closed-loop visits. From 1930 h on day 1 and every 15 min, a research nurse initiated a control cycle. The nurse inputted the sensor glucose value into the computer-based algorithm, the algorithm calculated the basal infusion rate, and the nurse adjusted the insulin pump accordingly. This procedure was continued for 36 h. Prandial insulin boluses were delivered according to the subject's standard practice, using his or her individual pump bolus calculator and finger-stick glucose levels. The algorithm was initialized using the subject's weight, total daily insulin dose (mean of previous 3 days), and 24-h basal insulin profile as programmed on the pump. Additionally, the algorithm was provided with sensor glucose levels measured during a 30-min period preceding the start of closed-loop delivery, the carbohydrate content of main meals, and prandial insulin boluses. Information on snacks and physical activity was not provided to the algorithm. The algorithm adapted itself to a particular subject by updating two model parameters: *1*) an endogenous glucose flux correcting for errors in model-based predictions and 2) carbohydrate bioavailability. Several competing models differing in the absorption of subcutaneous insulin and oral carbohydrates ran in parallel (17). The algorithm aimed to achieve glucose levels between 105 and 130 mg/dL and adjusted the actual level depending on fasting versus postprandial status and the accuracy of model-based glucose predictions. Safety rules limited maximum insulin infusion and suspended insulin delivery at a sensor glucose level ≤75 mg/dL or when the sensor glucose level was rapidly decreasing. Control algorithm versions 0.03.01–0.03.07 were used (8,9). Only initialization parameters were entered for each subject; the principles of the control approach and the main algorithm parameters remained unchanged across all versions tested.

Sampling and assays

Venous blood samples were collected for the measurement of glucose and insulin

concentrations every 30 min during the day and hourly overnight, but these were not used to calculate insulin requirements. Additional venous samples were taken every 15 min when plasma glucose was ≤70 mg/dL. Plasma was immediately separated by centrifugation. Plasma glucose levels were determined in real time by a YSI2300 STAT Plus analyzer (Yellow Springs Instruments, Farnborough, U.K.) but were not used to inform the algorithm. Plasma insulin concentration was measured by immunochemiluminometric assay (Invitron, Monmouth, U.K.) (intra-assay coefficient of variation 4.7%, interassay coefficient of variation 7.2–8.1%). Insulin aspart demonstrated 100% cross-reactivity in this assay.

Sample size, randomization, and masking

Based on previous data (8), we anticipated that closed-loop basal insulin delivery would increase the percentage of time when plasma glucose levels would be within the target range (71–180 mg/dL) by 37 (40)%. We calculated that 12 subjects would provide 80% power at the 5% level of significance to detect this difference compared with conventional insulin pump therapy. After informed consent and assent, the randomization procedure used a computer-generated allocation sequence, with permuted blocks placed in sealed envelopes. Investigators had access to plasma glucose levels for safety reasons, but subjects remained masked to plasma and sensor glucose data.

Statistical analysis

Senior investigators and study statisticians agreed on the analysis plan in advance. The primary outcome was the time with plasma glucose levels within the target range (71–180 mg/dL) over a 32-h period from 2400 h on day 1 to 0800 h on day 3. Secondary outcomes included mean plasma glucose, time when glucose concentration was ≤70 mg/dL (hypoglycemia), time when glucose concentration was >180 mg/dL (hyperglycemia), time with plasma glucose levels between 70 and 145 mg/dL overnight from 2400–0800 h, mean rate of insulin infusion, and mean plasma insulin concentrations. Low blood glucose index was used to assessed the duration and extent of hypoglycemia and was calculated using transformed glucose measurements that penalized progressively low glucose levels (18).

Parents of one subject withdrew consent; thus, the subject did not complete the study and was excluded from the analysis. For each outcome, a repeated-measures regression model based on the ranked normal transformation (except for the mean glucose concentration, which was not transformed because it already had an approximate normal distribution) was fitted to compare the two treatments, adjusting for plasma glucose level at the start of closed-loop treatment and for period effect. Analyses were conducted with SAS version 9.2 (SAS Institute, Cary, NC) statistical software. Outcomes were calculated using time-weighted data by GStat version 1.1.2 (University of Cambridge, Cambridge, U.K.) software. Kernel density of time-weighted plasma glucose was estimated using the package "nonparametric kernel smoothing methods for mixed data types" version 0.40-1, adopting a bandwidth of 0.25 mmol/L and implemented in the R version 2.11.1 (The R Foundation for Statistical Computing). Results are presented as median (interquartile range) or mean (SD), unless stated otherwise.

RESULTS

Participants

Twelve adolescents completed the study (5 males, age 15.0 [1.4] years, HbA_{1c} 7.9 [0.7]% [63 (16) mmol/mol], BMI 21.4 [2.6] kg/m^2). Subjects' baseline characteristics are shown in Supplementary Table 1.

Day-and-night glucose control

Plasma glucose, insulin delivery, and plasma insulin during conventional insulin pump therapy and closed-loop basal insulin delivery are shown in Fig. 1. When compared with standard pump therapy, time when plasma glucose was in the target range increased during closed-loop basal insulin delivery from 49% (26–79%) to 84% (78–88%) (P = 0.02) (Table 1). The mean plasma glucose concentration was significantly reduced from 165 (55) to 128 (20) mg/dL (P = 0.02). No difference was found in the time spent in the hypoglycemic range ≤70 mg/dL (P = 0.85) or the hyperglycemic range >180 mg/dL (P = 0.15). However, closed-loop basal insulin delivery reduced the time spent in hyperglycemia >300 mg/dL (P = 0.03). Distribution of plasma glucose levels over the 32-h evaluation period during the 2 treatment periods is illustrated in Supplementary Fig. 2.

Closed-loop basal insulin delivery achieved consistent outcomes across all subjects (Fig. 2). The range of mean plasma glucose levels was considerably tighter (107–161 vs. 85–258 mg/dL closed-loop versus conventional pump therapy, respectively). Similar observations applied to the time spent in the target range.

Insulin infusion rates, excluding prandial insulin delivery, were higher during closed-loop delivery (1.1 [0.9–1.7] vs. 0.9 [0.7–1.4] units/h, P = 0.006), resulting in an increased overall insulin delivery (P = 0.04) and reflected by higher mean plasma insulin concentration (P = 0.02).

Table 2 separates outcomes during the night (2400–0800 h) and day (0800–2400 h on day 2). Plasma glucose levels were in the target range 100% of the time for 17 of 24 nights during closed-loop insulin delivery. Mean overnight glucose levels were reduced during closed-loop versus conventional pump therapy. Time in target during the day favored closed-loop basal insulin delivery. Time spent in hypoglycemia was comparable between these periods and similar to the overall 32-h data. Insulin infusion rates were higher during closed-loop delivery both during the day and during the night and was associated with higher plasma insulin concentrations at night but not during the day. Study outcomes during morning, afternoon, evening, and periods of exercise are summarized in Supplementary Table 2 and Supplementary Fig. 3.

Sensor accuracy

The median relative absolute difference of the Dexcom continuous glucose monitor was 14.7% (7.0–25.3%). Clarke error grid analysis (19) showed that 97.6% of the values were in zones A and B, 0.5% in zone C, 1.9% in zone D, and 0.1% in zone E.

Hypoglycemia

Timing and level of hypoglycemia are illustrated in Fig. 1*A*. Ten episodes of hypoglycemia <55 mg/dL requiring treatment were documented during conventional insulin pump therapy and nine during closed-loop basal insulin delivery. One nocturnal hypoglycemic event occurred during conventional therapy, and none occurred during closed-loop delivery. All but one of the daytime episodes during closed-loop basal insulin delivery were associated with symptoms. During closed-loop therapy, four hypoglycemia events occurred within 2.5 h of breakfast or dinner, and five episodes occurred after exercise.

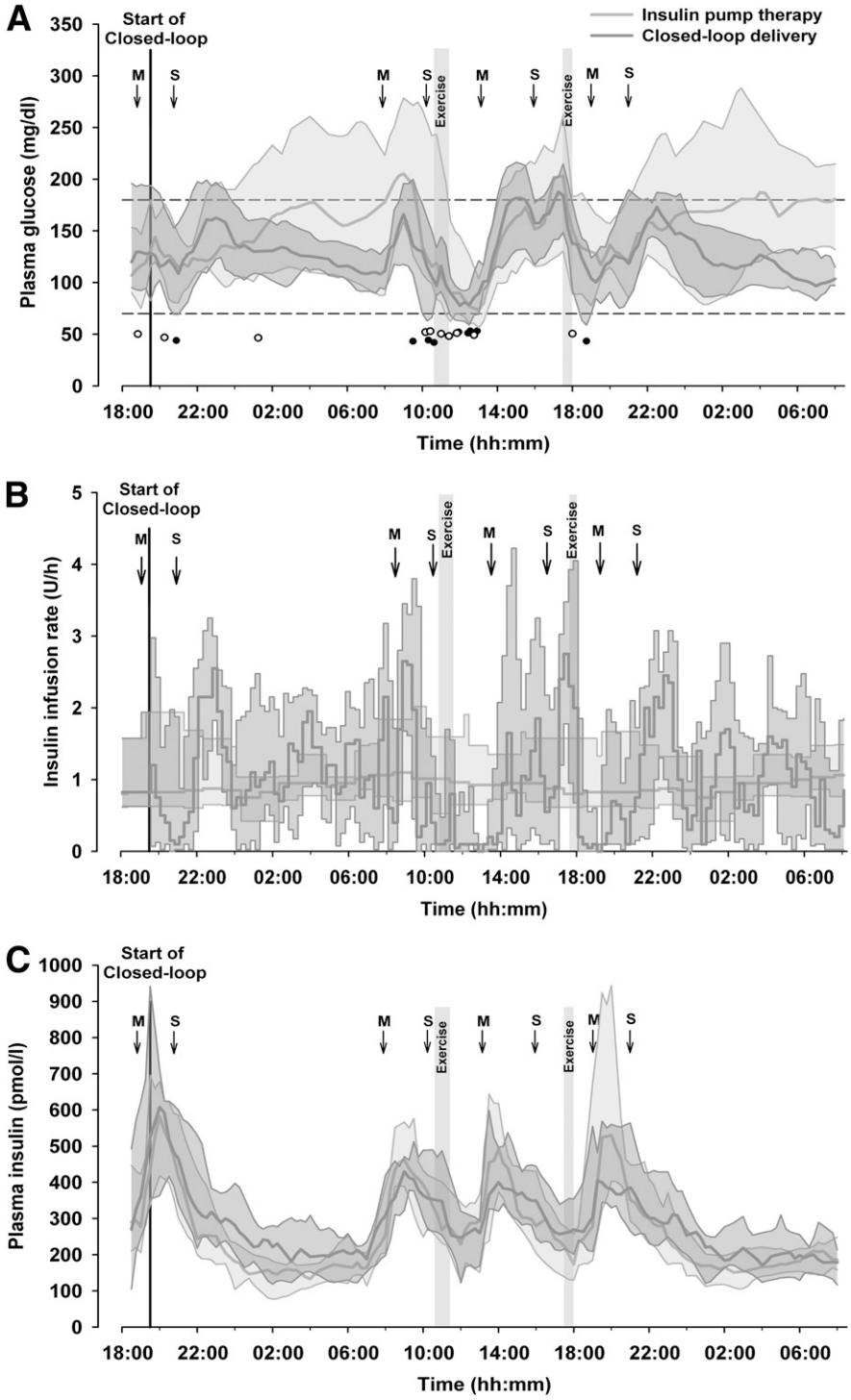

Figure 1—*Plasma glucose* (A)*, insulin infusion rates* (B)*, and plasma insulin* (C) *for conventional insulin pump therapy and closed-loop basal insulin delivery (median [interquartile range]). Meals (M), snacks (S), and exercise sessions are indicated.* A*: Episodes of hypoglycemia requiring treatment* (○*, insulin pump therapy;* ●*, closed-loop delivery).*

Physical activity energy expenditure

Mean PAEE over 32 h from 2400 h on day 1 to 0800 h on day 3 was identical during the two study visits (22 [7] kJ/kg/day) (Supplementary Fig. 4). PAEE over a 24-h period tended to be higher and more variable at home than that during study visits (38 [21] vs. 29 [9] kJ/kg).

CONCLUSIONS—We present the first randomized study to our knowledge reporting clinically significant lowering of mean plasma glucose over 32 h, suggesting that day-and-night closed-loop basal insulin delivery may improve glucose control in adolescents with type 1 diabetes. Time in target ≥70% threshold was recorded in all subjects during closed-loop basal insulin delivery, whereas during conventional pump therapy, only one third of participants presented a comparable outcome. If extrapolated to long-term control, the improved glucose levels could represent a ≥1% fall in HbA_{1c} (20).

Closed-loop basal insulin delivery during the night was particularly beneficial. We observed a 100% time in target for glucose levels during 17 of 24 nights. Plasma glucose was 76–95% of the time in the tighter glucose range from 71–145 mg/dL during the 2 study nights. This compares well with our previous investigations of overnight closed-loop insulin delivery using a similar control algorithm but different off-the-shelf glucose sensors (8,9). Only on 3 of 24 nights were plasma glucose levels ≤70 mg/dL. This level of control was achieved because the algorithm increased total overnight insulin delivery after the evening snack, where there was no accompanying insulin bolus, and maintained glucose control throughout the night.

During waking hours, benefits of closed-loop basal insulin delivery were present but less pronounced possibly because of the use of comparable approaches to prandial insulin delivery, which normally constitutes ~50% of total daily insulin dose. Hyperglycemia >300 mg/dL was reduced, confirming the ability of the closed-loop approach to limit long periods of excessive glucose levels. Prandial insulin boluses were slightly reduced, and this likely results from lower prebreakfast glucose levels during closed-loop basal insulin delivery. However daytime control was challenged by moderate-intensity exercise and by prandial insulin boluses calculated using the standard insulin bolus calculator, which although convenient, may have limited accuracy. In three instances, prandial insulin boluses were too large, possibly as a result of acutely overestimated insulin-to-carbohydrate ratios, and hypoglycemia occurred, despite reduction of basal insulin delivery by 30, 60, or 100% compared with the preprogrammed rate. Preemptive reduction of prandial boluses during closed-loop delivery could have decreased the risk of postprandial hypoglycemia, but complete omission of prandial

Table 1—*Study outcomes over 32 h from 2400 h on day 1 to 0800 h on day 3 based on plasma glucose levels*

Outcome	Insulin pump therapy (n = 12)	Closed-loop delivery (n = 12)	P
Primary outcome			
Time in target of 71–180 mg/dL (%)	49 (26–79)	84 (78–88)	0.02
Secondary outcomes			
Mean (SD) glucose (mg/dL)	165 (55)	128 (19)	0.02
SD of glucose (mg/dL)	48 (33–53)	36 (32–41)	0.09
Time in target of 71–145 mg/dL (%)	34 (20–58)	65 (57–75)	0.002
Hypoglycemia			
≤70 mg/dL (%)	3.8 (0.0–9.4)	4.5 (2.2–7.0)	0.85
≤63 mg/dL (%)	2.3 (0.0–3.6)	2.2 (1.4–4.9)	0.66
Low blood glucose index	0.9 (0.2–1.5)	1.3 (0.6–2.0)	0.23
Hyperglycemia			
>180 mg/dL (%)	40.1 (1.9–69.3)	9.6 (5.0–15.6)	0.15
>300 mg/dL (%)	0.0 (0.0–7.8)	0.0 (0.0–0.0)	0.03
Insulin infusion	0.9 (0.7–1.4)	1.1 (0.9–1.7)	0.006
Insulin concentration (pmol/L)	255 (226–279)	273 (231–316)	0.02
Insulin boluses (units)	24.5 (22.2–28.2)	21.2 (20.3–25.8)	0.04
Total insulin (units)	54.0 (46.8–72.9)	56.8 (51.8–78.7)	0.04

Data are median (interquartile range) unless otherwise indicated.

boluses as adopted by some fully closed-loop approaches is unlikely to be sufficiently effective (12) given delays associated with the absorption of rapid-acting analogs (5). Supplementary Fig. 5 shows an example of a hypoglycemic event that occurred 2 h after the evening meal during closed-loop therapy. The subject's premeal glucose level was 137 mg/dL; thus, 16 U insulin was administered 10 min before a meal of 80 g carbohydrates. Closed-loop delivery started 30 min after the meal and directed 0.08 U insulin over 90 min, compared with 3.06 U that would have been delivered during conventional treatment, before hypoglycemia of 44 mg/dL occurred and was treated by 30 g oral carbohydrates. Insulin delivery was gradually reestablished by closed-loop therapy 1 h after the hypoglycemic episode was treated, allowing euglycemia to be maintained overnight.

We tried to reproduce a typical exercise pattern, including walks, play during school breaks, and after-school activities, and did not announce these activities to the control algorithm. We achieved comparable glucose control during and after the moderate-intensity exercise on the two study visits; however, it was associated with hypoglycemia in some subjects. Physical activity causes rapid changes in insulin sensitivity (21), leading to glucose drops of variable magnitude. On five occasions, and particularly after the longer morning exercise, the closed loop was unable to arrest despite reducing or fully suspending insulin delivery. Unlike during conventional pump therapy, snacks preceding exercise did not fully alleviate the risk of hypoglycemia because the closed loop responded by increasing insulin delivery before exercise. The main benefits of not announcing exercise are reduced burden, ease of operation, and addressing compliance and adherence concerns that are pronounced in adolescents (22). Reducing time between closed-loop adjustments could accelerate recognition of an exercise-related drop in sensor glucose levels, but this is unlikely to be effective given the extended action of already-delivered insulin. Announcement of exercise to the algorithm at ≥30 min may be required to achieve improved outcomes and to reduce the risk of hypoglycemia.

Further challenges were related to the magnitude and duration of sensor errors. Overall accuracy expressed as the median absolute relative difference did not differ from that reported by the manufacturer (14.7 vs. 13%) and by others (23). However, up to 5-h periods of sensor overestimation by ≥60 mg/dL were observed and led to one postprandial hypoglycemic episode. Sensor overreading is of particular concern because insulin overdelivery may occur and increase the risk of hypoglycemia. Prolonged errors of large magnitude occur infrequently, but computer simulators, once appropriately validated (24), may allow preclinical assessment of safety of control algorithms under such infrequent, but critical conditions (25).

Previous studies reported by Steil et al. (13) evaluated a fully automated closed-loop system over a day-and-night period but without physical activity and snacks. Using a proportional integral derivative algorithm, plasma glucose levels were within the target range 75% of the time. Postprandial hyperglycemia and delayed hypoglycemia were observed and reduced in follow-up studies with the use of small prandial priming insulin boluses (12). Further modifications were made to reduce insulin delivery at elevated projected plasma insulin levels (26). Alternative closed-loop approaches include coadministration of glucagon to

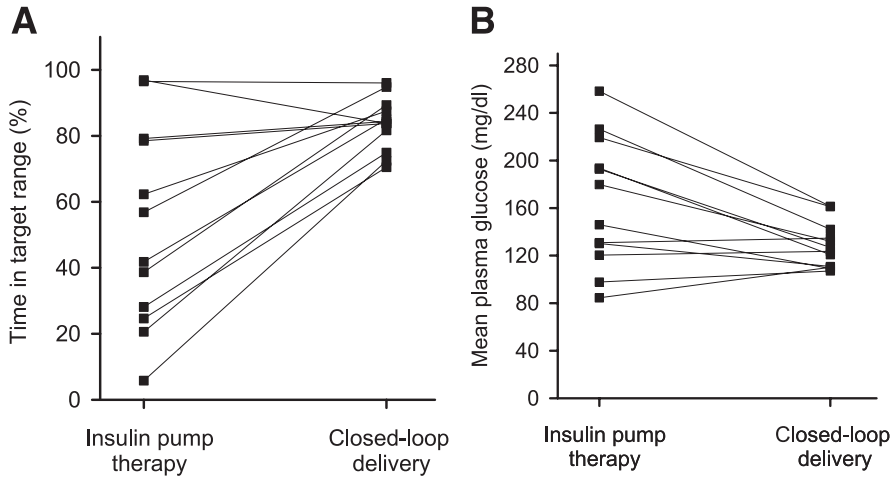

Figure 2—*Time when plasma glucose levels are within the target range of 71–180 mg/dL* (A) *and mean plasma glucose levels* (B) *during conventional insulin therapy and closed-loop delivery.*

Table 2—*Study day-and-night outcomes based on plasma glucose levels*

Outcome	First night		Daytime		Second night	
	Insulin pump therapy (n = 12)	Closed-loop delivery (n = 12)	Insulin pump therapy (n = 12)	Closed-loop delivery (n = 12)	Insulin pump therapy (n = 12)	Closed-loop delivery (n = 12)
Time in target of 71–180 mg/dL (%)	56 (12–85)	100 (96–100)	54 (37–81)	70 (65–79)	42 (0–85)	100 (99–100)
Mean (SD) glucose (mg/dL)	170 (71)	124 (22)	155 (49)	136 (22)	180 (69)	118 (25)
SD of glucose (mg/dL)	22 (13–30)	17 (13–19)	53 (35–60)	44 (38–48)	21 (14–36)	17 (10–20)
Time in target of 71–145 mg/dL (%)	28 (0–54)	76 (52–95)	47 (24–53)	52 (38–60)	26 (0–67)	95 (59–99)
Hypoglycemia						
≤70 mg/dL (%)	0.0 (0.0–0.4)	0.0 (0.0–0.0)	7.5 (0.0–12.3)	8.9 (4.4–11.9)	0.0 (0.0–9.9)	0.0 (0.0–0.0)
≤63 mg/dL (%)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	3.5 (0.0–7.2)	4.4 (2.8–8.2)	0.0 (0.0–2.2)	0.0 (0.0–0.0)
Low blood glucose index	0.0 (0.0–0.5)	0.2 (0.0–0.8)	1.6 (0.3–2.3)	2.0 (0.9–2.6)	0.0 (0.0–1.5)	0.4 (0.1–1.2)
Hyperglycemia						
>180 mg/dL (%)	35.0 (0.0–88.4)	0.0 (0.0–0.0)	31.2 (3.7–55.9)	18.5 (9.9–24.9)	49.9 (0.0–100.0)	0.0 (0.0–0.0)
>300 mg/dL (%)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–11.8)	0.0 (0.0–0.0)	0.0 (0.0–2.3)	0.0 (0.0–0.0)
Insulin infusion (units/h)	0.9 (0.8–1.1)	1.3 (0.8–1.7)	0.9 (0.7–1.6)	1.1 (0.8–1.8)	0.9 (0.8–1.1)	1.1 (0.9–1.4)
Insulin concentration (pmol/L)	170 (140–195)	228 (157–282)	336 (297–367)	323 (289–405)	171 (142–218)	205 (164–249)

Data are median (interquartile range) unless otherwise indicated. Daytime is defined as 0800–2400 h on day 2 and nighttime as 2400 h on day 1 to 0800 h on day 2 for the first night and 2400 h on day 2 to 0800 h on day 3 for the second night.

counteract delayed or excessive insulin action (27–29). Practical limitations associated with dual infusion apply.

The novelty of the present work is in testing closed-loop basal insulin delivery during common daily activities, including moderate-intensity exercise, eating snacks not accompanied by insulin boluses, and relying on a single sensor calibrated according to the manufacturer's instructions in preparation for home testing. The study was designed to replicate a typical school day of adolescents who often eat snacks not accompanied by insulin after school and then engage in moderate physical activity, such as playing outside or attending after-school clubs. It could be argued that if we accompanied snacks with insulin boluses, we could cause additional hypoglycemia after early evening exercise, causing a disadvantage to the conventional treatment. Similar reasoning about habitual behavior of adolescents applies to evening snacks and concurs with reports that missing insulin boluses is a common occurrence in adolescents (30,31) that disagrees with treatment guidelines. Treatment guidelines are difficult to impose in this particular age group and the result is prolonged hyperglycemia, as observed in the current study. Future study designs may consider whether evening snacks may be omitted during closed-loop basal insulin delivery given that the risk of nocturnal hypoglycemia is mitigated through insulin-responsive insulin delivery. Asymmetric study designs may be more reflective of anticipated clinical use of closed-loop systems than of conventional pump therapy.

Subjects were representative of a typical population of adolescents with type 1 diabetes. They were recruited from three nationally leading pediatric diabetes clinics, and their conventional treatment, not optimized for the purposes of this study, reflected typical glucose control that served as an adequate comparator to access benefits of closed-loop basal insulin delivery. This is further strengthened by a comparable HbA_{1C} (7.9 vs. 7.9%) and time in target range (48 vs. 47%) in adolescents/young adults at baseline of the JDRF Continuous Glucose Monitoring study (32).

We demonstrated that despite periods of suboptimal sensor accuracy, closed-loop basal insulin delivery may improve glucose control without increasing the risk of hypoglycemia. The drawbacks are that we were not able to prevent hypoglycemia during waking hours and that physical activity did not fully reproduce home patterns characterized by a higher mean and higher variability of energy expenditure. An additional drawback is that basal insulin delivery rates were changed manually and automation, though technologically feasible, was not used.

In conclusion, day-and-night closed-loop basal insulin delivery using off-the-shelf devices and an adaptive control algorithm may improve glycemic control in adolescents with type 1 diabetes. Unannounced moderate-intensity exercise and prandial insulin overdosing pose challenges to hypoglycemia-free closed-loop basal insulin delivery. Closed-loop systems may represent a tangible treatment option for young people with type 1 diabetes, improving glucose control during adolescence.

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D.E. and J.M.A. were responsible for screening and enrollment of subjects and arranged informed consent from the subjects. D.E., J.M.A., K.K., L.L., and K.C. provided patient care, collected the clinical and laboratory data, and contributed to biochemical analysis. D.E., J.M.A., H.R.M., M.E.W., C.L.A., D.B.D., and R.H. designed the studies. D.E., M.N., P.C., C.K., A.H., and R.H. carried out or supported the data analysis, including the statistical analyses. D.E., H.R.M., C.L.A., D.B.D., and R.H. contributed to the interpretation of the results and the writing and critical review of the manuscript. M.E.W. carried out randomization. R.H. coordinated the study and designed and implemented the glucose controller. D.E. and R.H. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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