Feasibility of Closed-Loop Insulin Delivery in Type 2 Diabetes: A Randomized Controlled Study

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OBJECTIVE

Closed-loop insulin delivery offers a promising treatment option, but to date, it has only been evaluated in type 1 diabetes. Our aim was to evaluate the feasibility of fully closed-loop subcutaneous insulin delivery in insulin-naïve patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Twelve subjects (seven males, age 57.2 years, BMI 30.5 kg/m^2) with noninsulin-treated type 2 diabetes (HbA_{1c} 8.4% [68 mmol/mol], diabetes duration 7.6 years) underwent two 24-h visits (closed-loop and control) in a randomized crossover design. During closed-loop visits, the subjects' routine diabetes therapy was replaced with model predictive control algorithm-driven subcutaneous insulin pump delivery based on real-time continuous glucose monitoring. Meals were unannounced, and no additional insulin was administered for carbohydrates consumed. During control visits, the usual diabetes regimen was continued (metformin 92%, sulfonylureas 58%, dipeptidyl peptidase-4 inhibitors 33%). On both visits, subjects consumed matched 50- to 80-g carbohydrate meals and optional 15-g carbohydrate snacks and remained largely sedentary. Plasma glucose measurements evaluated closed-loop performance.

RESULTS

Compared with conventional therapy, 24 h of closed-loop insulin delivery increased overall the median time in target plasma glucose (3.9–8.0 mmol/L) from 24 to 40% (P = 0.016), despite sensor under-reading by a median of 1.2 mmol/L. The benefit of the closed-loop system was more prominent overnight, with greater time in target glucose (median 78 vs. 35%; P = 0.041) and less time in hyperglycemia (22 vs. 65%; P = 0.041). There was no hypoglycemia during either intervention.

CONCLUSIONS

A closed-loop system without meal announcement and using subcutaneous insulin delivery in insulin-naïve patients with type 2 diabetes appears feasible and safe. Improvement in postprandial glucose control may require further optimization of system performance.

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Conventional insulin regimens for managing type 2 diabetes often result in suboptimal glycemic control, which is associated with an increased risk of diabetes-related comorbidities (1). The emergence of minimally invasive continuous glucose monitoring devices and newer insulins offer promising therapeutic options. Continuous glucose monitoring, that is, measuring interstitial glucose in real time, has several advantages over intermittent blood glucose testing, including early detection of impending hypoglycemia, but still requires interpretation with subsequent manual adjustment of insulin regimens.

The use of a closed-loop system that combines continuous glucose monitoring with automated algorithm-driven insulin delivery can potentially improve glycemic control (2). The control algorithm translates in real time information received from continuous glucose monitoring and computes the amount of insulin to be delivered subcutaneously by a pump (3). Such a system has been shown to be safe and efficacious in controlled overnight studies in adults with type 1 diabetes (4,5). Feasibility of daytime use of closed-loop insulin delivery has also been demonstrated in adolescents and pregnant women with type 1 diabetes (6,7). To our knowledge, no studies have evaluated closed-loop systems in type 2 diabetes. The closed-loop system may be of significant benefit in glycemic management of such patients in the hospital but, to date, has only been evaluated in intensive care patients receiving intravenous insulin with intravenous or subcutaneous glucose measurements (8,9). The aim of the present study was to evaluate the feasibility of 24 h of fully closed-loop glucose control in insulin-naïve patients with type 2 diabetes through subcutaneous continuous glucose sensing and subcutaneous insulin delivery.

RESEARCH DESIGN AND METHODS

Between October 2011 and July 2012, participants were recruited from the adult diabetes and metabolism clinics at Addenbrooke's Hospital, Cambridge, U.K. Inclusion criteria were age ≥18 years, type 2 diabetes treated with glucose-lowering medications, and HbA_{1c} of 7–10% [53–86 mmol/mol]. Exclusion criteria were type 1 diabetes, current insulin therapy, diet control alone, pregnancy, and proliferative retinopathy. The study had a randomized, two-period, crossover design. The protocol was approved by the regional ethics committee (South Birmingham Research Ethics Committee 11/WM/0150), and participants gave informed consent.

Participants attended the research facility for two 24-h visits (closed-loop and control) 1–6 weeks apart. On arrival, a FreeStyle Navigator continuous glucose monitoring system (Abbott Diabetes Care, Alameda, CA) with a 1-h warm-up time (10) was inserted and calibrated with capillary fingerstick glucose measurements according to the manufacturer's instructions. A peripheral intravenous cannula was inserted for plasma glucose and insulin sampling.

Closed-Loop Visit

Participants' usual diabetes treatment was withheld on the day of study. On arrival, a subcutaneous cannula was inserted in the abdomen for delivery of insulin lispro (Humalog; Eli Lilly, Indianapolis, IN) by a study pump (Animas 2020; Johnson & Johnson, New Brunswick, NJ). From 0900 h on day 1 until 0900 h on day 2, basal insulin rates were manually adjusted every 15 min on the basis of continuous glucose monitoring and advice of a model predictive control algorithm (versions 0.03.20–0.03.23) adapted from our previous work in type 1 diabetes (4,11). The algorithm was initialized with the participant's weight. No prandial insulin boluses were delivered, and the algorithm did not account for timing or carbohydrate content of meals. The algorithm adapted itself to a particular participant by updating a model parameter representing an error (glucose flux) in model-based predictions and refining the participant's insulin requirements. Several competing models differing in the rate of absorption of subcutaneous insulin were run in parallel (12). The algorithm aimed to achieve glucose levels between 5.8 and 7.2 mmol/L and adjusted the actual target level depending on the accuracy of the model-based glucose predictions and prevailing glucose levels. Safety rules limited maximum insulin infusion and suspended insulin delivery at a sensor glucose level of ≤4.2 mmol/L or when the sensor glucose level was rapidly decreasing.

Control Visit

During control visits, participants continued their usual glucose-lowering medications.

Meals and Activity

Standardized mixed meals were consumed at 0900 h (50 g carbohydrates), 1300 h (80 g carbohydrates), and 1800 h (60 g carbohydrates), with optional 15-g carbohydrate snacks, matched on both interventions. Breakfast was cereal with milk or toast with spread. Lunch choices were roast chicken, pork sausage, or lasagna and a dessert (apple crumble with custard or yogurt with fruit). The evening meal comprised a sandwich (egg, ham, or cheese filling) and a dessert (chocolate mousse or gelatin with fresh fruit). Snack options were cake, digestive biscuits, cheese and crackers, or fresh fruit consumed at 1100, 1500, and 2100 h. Decaffeinated tea or coffee was offered with all meals and snacks. Subjects remained largely sedentary during visits, with no physical activity scheduled.

Assays

Plasma glucose was measured by a YSI 2300 STAT Plus Analyzer (YSI, Fleet, Hampshire, U.K.). Plasma insulin was measured by immunochemiluminescence assay (Invitron, Monmouth, U.K.) (intra-assay coefficient of variance 4.7%, interassay coefficient of variance 7.2–8.1%), which has 100% cross-reactivity with insulin lispro.

Statistical Analysis

Power calculations were not performed for this early phase feasibility investigation. The primary outcome was the percentage of time spent with plasma glucose level in target range (3.9–8.0 mmol/L) from 0900 h on day 1 to 0900 h on day 2. Secondary outcomes were time spent above and below target, mean and SD of glucose level, plasma insulin level, and total insulin

dose analyzed for overall, overnight, and postmeal periods. Outcomes were evaluated for both plasma and sensor glucose levels. Paired sensor and plasma glucose values were used to assess FreeStyle Navigator accuracy. Paired fingerstick glucose and plasma glucose values assessed the accuracy of the FreeStyle Navigator built-in capillary glucose meter. Significant differences were determined by Wilcoxon signed rank test at $P \leq 0.05$. Analyses were conducted with GStat version 1.2 (University of Cambridge) and SPSS version 17 (IBM Corporation, Chicago, IL). Results are presented as mean ± SD or median (interquartile range).

RESULTS

Demographic Data

Sixteen patients were recruited. One patient did not meet inclusion criteria, and three were unwilling to complete both visits; hence, they were excluded from further analysis. Detailed baseline characteristics of the 12 patients who completed the study are summarized in Supplementary Table 1; 7 were male, and 10 were of white European and 2 of Indian ethnicity (mean age 57.2 ± 14.4 years, weight 88.3 ± 11.6 kg, BMI 30.5 ± 3.9 kg/m^2, diabetes duration 7.6 ± 6.1 years, HbA_{1c} 8.4 ± 0.8% [68 ± 9 mmol/mol]). Three participants were treated with a single glucose-lowering agent alone, and nine were taking two or more agents (metformin *n* = 11 [92%], sulfonylureas *n* = 7 [58%], dipeptidyl peptidase-4 inhibitors *n* = 4 [33%]).

Glycemic Control

Overall

The primary and secondary outcome data are summarized in Table 1. Closed-loop insulin delivery increased the primary outcome of time in target plasma glucose range (3.9–8.0 mmol/L) from 24% (2–43%) during control to 40% (30–64%, *P* = 0.016). Time spent >8.0 mmol/L was lowered from 76% (57–98%) to 60% (36–70%, *P* = 0.016). Mean plasma glucose concentration was similar (9.7 ± 1.4 vs. 9.4 ± 1.9 mmol/L, *P* = 0.480), and there was no time spent <3.9 mmol/L during either intervention. Plasma glucose SD, representing glucose variability, was higher during closed-loop delivery (1.8 ± 0.4 vs. 2.2 ± 0.7 mmol/L, *P* = 0.041). Plasma insulin concentration during closed-loop delivery was higher (167 [108–265] vs. 220 [164–343] pmol/L, *P* = 0.004); closed-loop insulin infusion was 1.2 (0.9–1.9) U/h. Figure 1 shows the profiles of plasma glucose, insulin infusion, and plasma insulin. A summary of secondary outcomes based on sensor glucose levels and sensor glucose profiles are provided in Supplementary Table 2 and Supplementary Fig. 1, respectively.

Overnight

After midnight, closed-loop insulin delivery increased time spent with plasma glucose in target (35% [2–71%] vs. 78% [48–97%], *P* = 0.041), time in hyperglycemia was reduced (65% [29–98%] vs. 22% [3–52%], *P* = 0.041), and mean plasma glucose was similar (8.6 ± 1.2 vs. 7.8 ± 1.5 mmol/L, *P* = 0.099) (Table 1). Median plasma glucose was in target overnight from 2200 h during closed-loop insulin delivery but remained elevated throughout most of the night during the control condition (mean 7.8 ± 1.5 mmol/L) (Fig. 1). Mean overnight sensor glucose level during closed-loop insulin delivery was 6.4 ± 1.4 mmol/L.

Postmeal

Meals consumed were matched on both study visits. All 12 participants chose to have a 15-g carbohydrate snack midmorning and before bedtime, whereas only 7 chose to have a midafternoon snack. After breakfast, 100% of participant time with glucose levels >8.0 mmol/L were recorded for both interventions (Table 2). Closed-loop insulin delivery increased time in target from 3% (0–25%) to 36% (0–45%) after lunch and from 7% (0–70%) to 41% (16–57%) after the evening meal. Average insulin infusion during closed-loop delivery after breakfast, lunch, and evening meal was 2.3 (1.9–2.7), 1.4 (0.8–2.0), and 1.3 (1.0–1.8) U/h, respectively.

Sensor Accuracy

The median relative absolute difference (RAD) between paired FreeStyle Navigator continuous glucose monitoring system and plasma glucose values (1,210 pairs) was 12.7%; the median bias was −1.2 mmol/L, indicating sensor under-reading. By Clarke error grid, 77% of paired values

Table 1—Study outcomes during overall and overnight study periods based on plasma glucose concentrations

	Overall (0900–0900 h)			Overnight (0000–0900 h)		
Outcome	Closed-loop	Control	*P* value	Closed-loop	Control	*P* value
Time in target glucose 3.9–8.0 mmol/L (%)	40 (30–64)	24 (2–43)	**0.016**	78 (48–97)	35 (2–71)	**0.041**
Glucose (mmol/L)	9.4 ± 1.9	9.7 ± 1.4	0.480	7.8 ± 1.5	8.6 ± 1.2	0.099
Starting glucose (mmol/L)	9.6 ± 2.2	9.7 ± 1.4	0.117	7.5 ± 2.8	8.1 ± 1.9	0.530
SD of glucose (mmol/L)	2.2 ± 0.7	1.8 ± 0.4	**0.041**	0.7 ± 0.3	0.7 ± 0.3	0.480
Glucose 3.9–10.0 mmol/L (%)	74 (59–85)	74 (38–79)	0.530	100 (94–100)	100 (69–100)	0.753
Glucose ≤3.9 mmol/L (%)	0 (0–0)	0 (0–0)	1.000	0 (0–0)	0 (0–0)	1.000
Low blood glucose index	0.0 (0.0–0.1)	0.0 (0.0–0.0)	0.066	0.0 (0.0–0.1)	0.0 (0.0–0.0)	0.208
Glucose >8.0 mmol/L (%)	60 (36–70)	76 (57–98)	**0.016**	22 (3–52)	65 (29–98)	**0.041**
Glucose >10.0 mmol/L (%)	27 (15–41)	26 (21–62)	0.530	0 (0–6)	0 (0–31)	0.753
High blood glucose index	5.5 (3.2–8.5)	5.6 (4.9–10.9)	0.638	1.6 (0.7–3.1)	3.1 (1.5–6.2)	0.209
Insulin infusion (U/h)	1.2 (0.9–1.9)	—	—	0.8 (0.3–1.2)	—	—
Plasma insulin (pmol/L)	220 (164–343)	167 (108–265)	**0.004**	111 (52–200)	99 (47–152)	**0.015**

Data are median (interquartile range) or mean ± SD. Boldface indicates significance at $P \leq 0.05$.

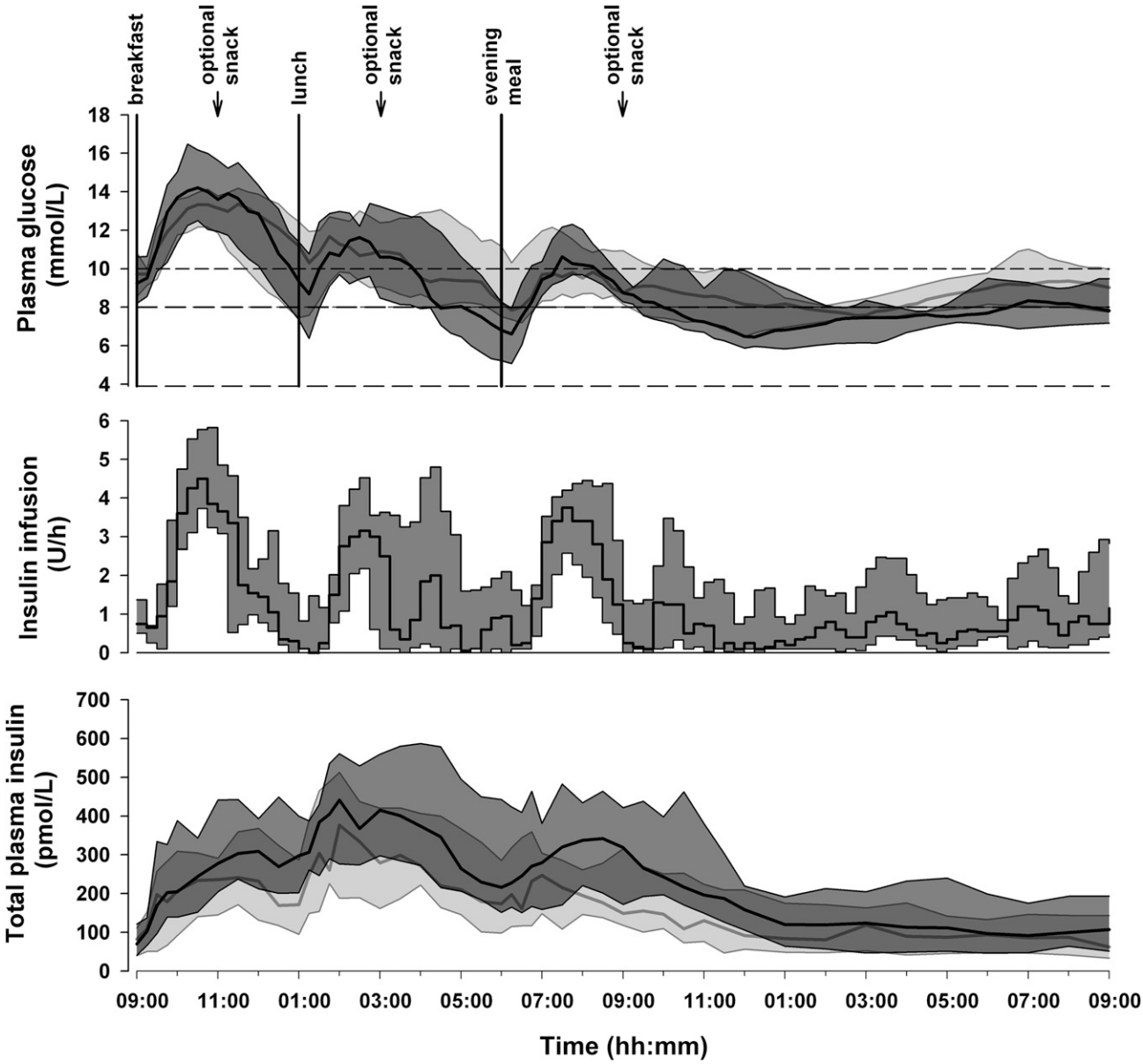

Figure 1—Profiles of plasma glucose concentration, insulin infusion rates, and total plasma insulin concentration for closed-loop insulin delivery (black line) and control (gray line) visits (median [interquartile range]). Meals and snacks are indicated.

were in zone A and 22% in B (Supplementary Fig. 2). An evaluation of the accuracy of the FreeStyle Navigator capillary fingerstick measurements compared with plasma glucose level (109 pairs) showed a median RAD of 11.5% and median bias of −0.9 mmol/L.

CONCLUSIONS

In this cohort of insulin-naïve patients with type 2 diabetes, 24 h of closed-loop insulin delivery increased overall plasma glucose time in target and reduced hyperglycemia without any risk of hypoglycemia. After midnight, the benefit of the closed-loop system was more prominent, with a doubling of glucose time in target and mean overnight plasma glucose levels (7.8 mmol/L) consistent with current recommended premeal targets (13). The average plasma glucose level during conventional therapy was higher (8.6 mmol/L), which is relevant because fasting hyperglycemia is independently associated with increased inpatient mortality (14). Overnight glycemic control achieved with the closed-loop system was comparable to that previously shown in adults with type 1 diabetes (time in target 78 vs. 76%) (4).

The relatively modest improvement in daytime glycemic control could be attributed to postprandial hyperglycemia. The postbreakfast period was most challenging, with no improvement in glucose concentration observed during closed-loop intervention despite the administration of a median of 9.2 U insulin. Reasons for this included commencement of the algorithm at the time of eating breakfast (algorithm may take up to 4 h to become fully effective as a result of delays in

Table 2—Plasma glucose outcomes evaluated during postbreakfast, postlunch, and postevening meal periods

	Postbreakfast (0900–1300 h)		Postlunch (1300–1800 h)		Postevening meal (1800–0000 h)	
	Closed-loop	Control	Closed-loop	Control	Closed-loop	Control
Time in target glucose 3.9–8.0 mmol/L (%)	0 (0–14)	0 (0–11)	36 (0–45)	3 (0–25)	41 (16–57)	7 (0–70)
Glucose (mmol/L)	12.5 ± 2.4	11.9 ± 1.4	10.0 ± 2.7	10.4 ± 2.0	9.2 ± 2.2	9.3 ± 2.1
Glucose 3.9–10.0 mmol/L (%)	19 (2–41)	17 (3–46)	59 (18–87)	44 (9–88)	79 (68–99)	87 (45–100)
Time >8.0 mmol/L (%)	100 (86–100)	100 (8–100)	64 (55–100)	97 (75–100)	59 (43–84)	93 (30–100)
Time >10.0 mmol/L (%)	81 (59–98)	83 (54–97)	41 (13–82)	56 (13–91)	21 (2–32)	13 (0–55)
Insulin infusion (U/h)	2.3 (1.9–2.7)	—	1.4 (0.8–2.0)	—	1.3 (1.0–1.8)	—
Plasma insulin (pmol/L)	248 (187–352)	192 (146–305)	329 (301–508)	270 (180–403)	256 (182–437)	167 (104–259)

Data are median (interquartile range) or mean ± SD.

insulin kinetics [4,11], consumption of a sugar-rich 50-g carbohydrate breakfast meal, and initiation of insulin delivery through a newly inserted infusion cannula known to be associated with delayed insulin absorption [15]). Compared with the morning period, glucose levels were improved after lunch and the evening meal. This improvement can be attributed to increased effectiveness of closed-loop insulin delivery with longer duration of use; the algorithm continuously updates itself to participants in real time, using information on sensor glucose levels to predict future glucose excursions.

Biased sensor glucose measurements contributed to suboptimal plasma glucose levels. Overall, the 24-h mean sensor glucose level was 8.1 ± 1.7 mmol/L, but because under-reading of sensor glucose by 1.2 mmol/L occurred, higher plasma glucose levels of 9.4 ± 1.9 mmol/L were observed. The negative bias may explain the limited ability of the control algorithm to match insulin requirements because only sensor glucose information is used by the algorithm.

Although the fully closed-loop approach used in the present study facilitates easier application of such a system of insulin delivery, a hybrid or semi-closed-loop algorithm comprising meal announcement and additional bolus insulin before meals may overcome some of the lag in onset of insulin action (16). This approach requires additional user inputs, however, which may limit its usability in an inpatient setting. We opted for the fully closed-loop system without meal announcement given that the studied population of type 2 diabetic participants had functioning, albeit impaired, endogenous insulin secretion, which we anticipated to supplement with closed-loop insulin delivery, particularly in the early prandial period. The hyperglycemia observed may also be related to insulin resistance and considerably impaired residual endogenous insulin secretion specific to the cohort studied. Refinements to the algorithm may be required with a more responsive insulin delivery system, particularly in the morning.

Closed-loop insulin delivery did not improve glycemic variability as measured by SD of plasma glucose. This can be explained by the occurrence of both high and low glucose levels. The algorithm achieved lower premeal glucose values than did conventional therapy but had less of an effect on postprandial hyperglycemia. It is expected that the algorithm will reduce day-to-day variability, and further research is needed to establish the relationship between within-day or day-to-day glucose variability and its associated potentially adverse consequences (17).

The present study provided an objective evaluation of the performance of FreeStyle Navigator continuous glucose monitoring in type 2 diabetes, demonstrating comparable accuracy with a previous closed-loop study that used the same generation system in type 1 diabetes (median RAD 12.0%) (4) but less accuracy than a study in a mixed cohort of type 1 and 2 diabetes that evaluated different continuous glucose monitoring systems (median RAD 7.8%) (18). Under-reading of the FreeStyle Navigator built-in fingerstick measurements explains most of the inaccuracy in sensor glucose readings because these fingerstick values were used to calibrate the continuous glucose monitoring device.

Strengths of this study were the randomized crossover design, use of a commercially available insulin pump and continuous glucose monitoring, and application of a fully closed-loop system over 24 h with no additional inputs required for meals. The sensor was calibrated with fingerstick glucose level only at manufacturer-specified intervals. Initiation of the algorithm was simple, using body weight alone. Calculation of an appropriate starting dose of insulin can be challenging by conventional methods, particularly in insulin-naïve patients. Use of the subcutaneous route for both glucose sensing and insulin delivery is less invasive, hence offering a safer and potentially more convenient mode of treatment for inpatients compared with intravenous closed-loop insulin delivery applied in the intensive care setting (8,9).

Limitations of this study were the manual mode, which is associated with the risk of operator error and delay in adjusting the insulin pump but reducing the regulatory burden and system complexity, and short duration (24 h) of the closed-loop operation. Although glucose-lowering therapies were discontinued the evening prior, it is possible that some medications may have had a variable and persisting effect on glucose levels during closed-loop visits. These effects could be eliminated with the evaluation of closed-loop insulin delivery over multiple days.

Evaluation of otherwise healthy insulin-naïve diabetic patients alone limits applicability of the results to other patients with type 2 diabetes. Insulin-treated patients were excluded from the study because of a likely persisting effect of the longer-acting insulin preparations on glucose control, even when discontinued before closed-loop study visits.

In summary, this randomized controlled study is the first in our knowledge to evaluate a closed-loop system that uses subcutaneously delivered insulin to manage type 2 diabetes. In a cohort of insulin-naïve patients with type 2 diabetes, 24 h of fully closed-loop insulin delivery resulted in a modest improvement in overall glucose levels, with a greater benefit observed overnight, and no risk of hypoglycemia. Rapid excursions in blood glucose levels following meals, which were associated with delays in subcutaneous insulin absorption from interstitial fluid as well as sensor bias, reduced the effectiveness of daytime use of the closed-loop system. Larger studies evaluating closed-loop insulin delivery over a longer duration are warranted.

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Duality of Interest. M.E.W. has received license fees from Becton Dickinson and has patent applications. M.L.E. has received speaker honoraria from Eli Lilly and served on advisory panels for Medtronic, Sanofi, and Cellnovo. R.H. has received honoraria for speaking engagements from Medtronic, LifeScan, Novo Nordisk, and Eli Lilly; sits on the advisory panel for Animas; has received license fees from Becton Dickinson and B. Braun; and has patent applications. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. K.K. drafted the manuscript. K.K. and H.T. recruited participants. K.K., H.T., L.L., K.C., D.E., J.M.A., M.N., M.E.W., M.L.E., and R.H. approved the final version of the manuscript. K.K., H.T., L.L., K.C., D.E., and J.M.A. performed studies. K.K., H.T., and R.H. interpreted data. K.K. and M.N. analyzed data. K.K., M.E.W., M.L.E., and R.H. designed the study. H.T. and R.H. reviewed and edited the manuscript. R.H. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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