DIABETES TECHNOLOGY & THERAPEUTICS
Volume 16, Number 10, 2014

DOI: 10.1089/dia.2014.0050

DTT
Diabetes Technology & Therapeutics

ORIGINAL ARTICLE

Multicenter Closed-Loop/Hybrid Meal Bolus Insulin Delivery with Type 1 Diabetes

H. Peter Chase, MD,[1] Francis J. Doyle III, PhD,[2] Howard Zisser, MD,[3] Eric Renard, MD, PhD,[4] Revital Nimri, MD,[5] Claudio Cobelli, PhD,[6] Bruce A. Buckingham, MD,[7] David M. Maahs, MD,[1] Stacey Anderson, MD,[8] Lalo Magni, PhD,[9] John Lum, MS,[10] Peter Calhoun, MS,[10] Craig Kollman, PhD,[10] and Roy W. Beck, MD, PhD,[10] for the Control to Range Study Group

Abstract

Background: This study evaluated meal bolus insulin delivery strategies and associated postprandial glucose control while using an artificial pancreas (AP) system.

Subjects and Methods: This study was a multicenter trial in 53 patients, 12–65 years of age, with type 1 diabetes for at least 1 year and use of continuous subcutaneous insulin infusion for at least 6 months. Four different insulin bolus strategies were assessed: standard bolus delivered with meal ($n=51$), standard bolus delivered 15 min prior to meal ($n=40$), over-bolus of 30% delivered with meal ($n=40$), and bolus purposely omitted ($n=46$). Meal carbohydrate (CHO) intake was 1 g of CHO/kg of body weight up to a maximum of 100 g for the first three strategies or up to a maximum of 50 g for strategy 4.

Results: Only three of 177 meals (two with over-bolus and one with standard bolus 15 min prior to meal) had postprandial blood glucose values of <60 mg/dL. Postprandial hyperglycemia (blood glucose level >180 mg/dL) was prolonged for all four bolus strategies but was shorter for the over-bolus (41% of the 4-h period) than the two standard bolus strategies (73% for each). Mean postprandial blood glucose level was 15.9 mg/dL higher for the standard bolus with meal compared with the prebolus (baseline-adjusted, $P=0.07$ for treatment effect over the 4-h period).

Conclusions: The AP handled the four bolus situations safely, but at the expense of having elevated postprandial glucose levels in most subjects. This was most likely secondary to suboptimal performance of the algorithm.

Introduction

Studies using the artificial pancreas (AP) in patients with type 1 diabetes (T1D) offer the opportunity to evaluate the safety and efficacy of postprandial glucose control during closed-loop (CL) control. The American Diabetes Association recommends that glucose levels remain below 180 mg/dL at all times following a meal.[1] Unfortunately, the current rapid-acting insulins have been shown to be too slow in action to attain optimal postprandial glucose levels when given just

[1]Barbara Davis Center for Childhood, Aurora, Colorado.
[2]Department of Chemical Engineering, University of California, Santa Barbara, Santa Barbara, California.
[3]Sansum Diabetes Research Institute, Santa Barbara, California.
[4]Montpellier University Hospital, Department of Endocrinology, Diabetes, Nutrition and INSERM 1001 Clinical Investigation Center, the Institute of Functional Genomics, UMR CNRS 5203/INSERM U661, University of Montpellier, France.
[5]Jesse Z. and Sara Lea Shafer Institute for Endocrinology and Diabetes, National Center for Childhood Diabetes, Schneider Children's Medical Center of Israel and Sackler Faculty of Medicine, Tel-Aviv University, Tel Aviv, Israel.
[6]University of Padova, Padova, Italy.
[7]Stanford University, Stanford, California.
[8]University of Virginia, Charlottesville, Virginia.
[9]University of Pavia, Pavia, Italy.
[10]Jaeb Center for Health Research, Tampa, Florida.
The full listing of the members of the study group is included in the Appendix.
The study is listed registered at www.clinicaltrials.gov with clinical trial registration number NCT01271023.
The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the JDRF.

prior to eating. Excursions above 180 mg/dL are common in recent studies involving standard basal-bolus therapy[2,3] and CL systems, regardless whether a partial or full meal bolus is delivered by the controller[4–7] or omitted.[7–9]

Based on evidence that prebolusing for a meal reduces postprandial glucose excursions,[2] many diabetes physicians recommend that patients deliver their meal boluses 15–20 min prior to eating. Weinzimer et al.[7] compared a fully automated Medtronic (Northridge, CA) ePID CL system with a semi-automated hybrid system in which 25–50% of the meal bolus was administered 15 min prior to the meal. The mean daytime and peak postprandial glucose levels were significantly lower in the hybrid group compared with the group using the fully CL system ($P < 0.05$). It is important to determine how AP systems will respond to meals using the currently available rapid-acting insulins when the insulin is delivered with the meal or when delivered 15–20 min prior to the meal.

A second issue common to meal boluses relates to an excessive amount of insulin being administered. This happens when there is an overestimate of carbohydrate (CHO) to be eaten, or when an insulin dose is taken for a planned amount of food intake but less food is then eaten. It has even been suggested the insulin be given after the meal to preschoolers, who often have unpredictable eating patterns.[10] Because administration of excessive meal insulin is a frequent occurrence, it is important to determine how an AP system will handle such an over-bolus of insulin delivered with a meal.

A third issue, particularly with teenagers, is forgetting to give an insulin bolus to cover a meal[11,12] or a snack.[13] Missing two meal boluses per week over 3 months was associated within a 0.5% higher hemoglobin A1c level.[11] The AP system may represent the only method of assuring insulin coverage for all meals and snacks. It will thus be important to determine how the AP system will handle missed meal insulin boluses.

Breakfast is often the most difficult meal of the day to control postprandial glucose levels, in part because of high levels of counterregulatory hormones[14,15] as well as less suppression of endogenous glucose production. As part of a multicenter study to evaluate a control-to-range class AP system under a variety of conditions, the function of the system was evaluated in four breakfast-related situations likely to occur in real life, with insulin administered (1) just prior to the meal, (2) 15 min prior to the meal, or (3) with a 30% over-bolus or (4) when no meal bolus was administered (AP management only).

Research Design and Methods

This study was conducted at seven clinical centers. The protocol was approved by local Institutional Review Boards, and written informed consent was obtained from each patient or parent, with assent obtained as required. An independent Data and Safety Monitoring Board provided oversight. The full protocol is available online (www.clinicaltrials.gov/ct2/show/NCT01271023); key aspects are summarized herein.

Major eligibility criteria included 12–65 years of age, T1D for at least 1 year, use of an insulin pump for at least 6 months, and hemoglobin A1c level of 5.0–10.5%. Exclusions included current pregnancy, diabetic ketoacidosis in the prior 6 months, severe hypoglycemia with seizure or loss of consciousness in the prior 12 months, and the presence of any medical conditions, laboratory abnormalities, or medications that might limit study participation.

The devices used in the CL system were the Dexcom (San Diego, CA) Seven® Plus continuous glucose monitor (CGM) and the OmniPod® insulin management system (Insulet Corp., Bedford, MA). Two blinded sensors were inserted 2–3 days before the admissions. The more accurate sensor was used, but recording could be switched to the other sensor if it malfunctioned during the admission. The FreeStyle Lite® blood glucose meter (Abbott Diabetes Care, Alameda, CA) was used to calibrate the CGM device. The system was designed with a modular architecture consisting of a hardware platform (APS/Santa Barbara) to facilitate device communication and run AP algorithms, a safety supervision module (SSM/UVA-Santa Barbara) to reduce insulin administration in the event of predicted hypoglycemia, and a range correction module (RCM/Pavia-Padova) to administer correction insulin to maintain glucose concentration in the euglycemic range. In view of the relevant sensor error, the algorithm tries to maintain the CGM in the center of the range. The range controller (RCM) is based on model predictive control and uses a model with patient-specific tuning based on body weight, insulin basal rates, and total daily insulin. A predictive hypoglycemia prevention algorithm (SSM) was used to minimize the risk of hypoglycemia, displaying a red light to suggest preemptive CHO treatment when hypoglycemia was deemed unavoidable. A complete description of the integrated AP has been published elsewhere.[16–22]

Clinical research center protocol

The study protocol included up to four breakfast meals for each patient during which the same meal, consisting of 50% CHO, 20% protein, and 30% fat with 1 g of CHO/kg of body weight (maximum of 100 g of CHO for the first three bolus strategies listed below and a maximum of 50 g for the missed bolus) was eaten over approximately 15 min. Four different insulin bolus strategies were assessed:

1. Standard size bolus delivered at same time as meal
2. Standard size bolus delivered 15 min prior to meal
3. Over-bolus of 30% delivered at same time as meal
4. Bolus purposely omitted

For safety, if the subject was hyperglycemic (>200 mg/dL) at the time of the breakfast meal, the study physician could opt to serve an alternate low-CHO meal (<20 g) to prevent excessive postprandial hyperglycemia (used for five meals; see below). Breakfast with the standard size bolus delivered 15 min prior to meal was given at approximately 9 a.m., with CL control starting 30 min earlier; breakfast with the bolus purposely omitted was given at 7 a.m. the following day. Breakfast with the standard-size bolus delivered at the same time was given at approximately 9 a.m. on the second admission, with CL control starting 15 min earlier; breakfast with over-bolus was given at 7 a.m. the following day. Meal boluses were administered by the physician/nurse inputting the grams of CHO (as determined by the hospital dietitian) at the start of the meal, with automated bolus recommendation by the system based on the subject's home insulin to CHO (I/C) ratio and automated delivery of the bolus following confirmation of the recommendation. There was no pretuning of I/C ratios prior to

the study. Between-meal insulin dosing was driven by the automated CL controller. The CGM was calibrated using fingerstick values 30 min before each breakfast.

Plasma glucose level was measured using a YSI (Yellow Springs, OH) clinical laboratory analyzer instrument every 15 min for 90 min following breakfast and every 30 min at all other times. For plasma glucose levels of ≤60 mg/dL or if the Safety Monitoring System indicated impending hypoglycemia, treatment was given with approximately 16 g of glucose (juice or glucose tablets) and repeated as necessary (hypoglycemic rescue). The YSI plasma glucose level was measured every 15 min until the plasma glucose level exceeded 80 mg/dL. For plasma glucose levels of ≥300 mg/dL for more than 1 h, a correction bolus of insulin was recommended by protocol (hyperglycemic rescue).

Adverse event reporting included diabetic ketoacidosis, severe hypoglycemia, and any event requiring the assistance of another person due to altered consciousness to actively administer glucagon, insulin, or other resuscitative actions.

Statistical methods

For each of the four testing conditions, various glycemic metrics for hyperglycemia, hypoglycemia, and variability were computed from YSI measurements over the 4 h following breakfast and at the 4-h time point. Repeated-measures regression models were used to test the differences in continuous glycemic outcomes following the standard bolus at time of breakfast and the standard bolus prior to breakfast, accounting for correlated data from the same subject, adjusting for baseline blood glucose value.

Meals with an appropriate insulin bolus and the full 1 g of CHO/kg body weight content (up to 100 g) and at least 2 h of data with a YSI measurement 4 h after breakfast were included in the analyses (19 tests were not included: 12 had insulin boluses that were administered incorrectly, five had low-CHO content [<20 g] to prevent excessive postprandial hyperglycemia, two had <2 h of post-breakfast glucose data, and seven had a missing YSI measurement 4 h post-breakfast). Cases where external intervention was necessary to treat hypoglycemia or hyperglycemia not requested by the controller algorithm were handled by imputing glucose values of 60 mg/dL for 1 h following hypoglycemic treatment and values of 400 mg/dL for 2 h following hyperglycemic treatment so they would not artificially inflate the performance metrics (e.g., more values in target range than would have occurred in the absence of external intervention). All *P* values are two-sided, and analyses were performed using SAS version 9.3 software (SAS Institute, Cary, NC).

Results

The study included 177 tests involving breakfast periods from 53 participants with T1D: mean age, 28 years; mean glycated hemoglobin level, 7.9% (Supplementary Table S1; Supplementary Data are available online at www.liebertonline.com/dia). There were 51 breakfasts with standard boluses, 40 with an early-delivered standard bolus, 40 with an over-bolus, and 46 without a bolus. Table 1 provides the glycemic metrics during the 4 h following breakfast and at 4 h. Supplementary Tables S2 and S3 provide similar data stratified for adults and adolescents. Figures 1 and 2 both show the plasma glucose levels and insulin delivery over the 4-h post-breakfast period for each of the four testing conditions. Supplementary Figures S1 and S2 show the CGM levels and insulin delivery over the 4-h post-breakfast period. Supplementary Table S4 gives the CGM accuracy metrics. The median difference between CGM and YSI values was −8 mg/dL with a median relative absolute difference of 10%. Supplementary Table S5 gives intrasubject glycemic differences between standard bolus at time of breakfast and the other three breakfast scenarios. There were no cases of severe hypoglycemia, diabetic ketoacidosis, or other adverse events.

Standard bolus at time of breakfast

Following a standard bolus given at the start of breakfast, no meals had a required hypoglycemic rescue, and one had a required hyperglycemic rescue (Table 1). During the 4 h after a breakfast with a standard bolus, the glucose level rose above 400 mg/dL in 2% of meals, the median of each participant's mean glucose level was 204 mg/dL, the median percentage of glucose values 71–180 mg/dlL was 27%, and the median excursion was 121 mg/dl. At 4 h after the meal, 53% of meals had a glucose value in this range. The median of the area under the curve (AUC) 180 mg/dL was 34 mg/dL/min. The median cumulative basal plus bolus insulin over the 4 h was 10.4 units.

Standard bolus prior to breakfast

Following a standard bolus given 15 min prior to breakfast, one meal had a required hypoglycemic rescue, and none had a required hyperglycemic rescue (Table 1). During the 4 h after a breakfast with a premeal standard bolus, the glucose level did not rise above 400 mg/dL. The median of each participant's mean glucose level was 203 mg/dL, the median percentage of glucose values 71–180 mg/dL was 27%, and the median excursion was 105 mg/dL. At 4 h after the meal, 55% of meals had a glucose value in this range. The median of the AUC 180 mg/dL was 29 mg/dL/min. The median cumulative basal plus bolus insulin over the 4 h was 11.5 units. The median percentage of postprandial YSI values in-range (71–180 mg/dL) varied when the fasting glucose level was below 130 mg/dL (45% for the standard bolus and 55% for the prebolus), 131–180 mg/dL (18% for the standard bolus and 26% for the prebolus), and above 181 mg/dL (0% for standard bolus and prebolus) (Supplementary Table S6).

As seen in Table 1, outcome metrics appear similar for the standard bolus delivered with breakfast and 15 min prior to breakfast. However, it can be seen that by chance baseline glucose levels tended to be higher before the premeal bolus test than before the with-meal bolus test. Controlling for baseline glucose level, the time in range over the 4 h after breakfast was similar when the standard bolus was delivered at the time of breakfast compared with the standard bolus delivered prior to breakfast (treatment effect, −2.6%; 95% confidence interval, −15.3% to +10.0%; $P=0.68$). The treatment effect for mean glucose level over the 4 h was +15.9 mg/dL (95% confidence interval, −1.6 mg/dL to 33.4 mg/dL; $P=0.07$).

"Over-bolus" at time of breakfast

Following an over-bolus at the time of breakfast, one meal had a required hypoglycemic rescue, and two had a required hyperglycemic rescue (Table 1). During the 4 h after a breakfast with an over-bolus, the glucose level rose above 400 mg/dL in 5% of meals, the median of each participant's

Table 1. Glycemic Outcomes

	Standard bolus delivered with meal	*Standard bolus delivered before meal*	*Over-bolus delivered with meal*	*No bolus delivered with meal*
Number of participants	42	40	40	46
Number of breakfasts	51	40	40	46
Meal and insulin delivery characteristics				
Meal size (g of CHO)	68 (60, 78)	67 (58, 75)	63 (51, 75)	50 (50, 50)
Normalized meal size (g of CHO/kg of body weight)	1.00 (0.99, 1.00)	1.00 (0.98, 1.00)	0.99 (0.95, 1.00)	0.74 (0.64, 0.93)
Minutes from bolus to start of meal	0 (−2, +1)	−15 (−16, −14)	+1 (−1, +1)	—
Meal bolus size (U)	6.0 (5.2, 8.8)	6.0 (4.8, 9.5)	7.4 (6.0, 10.4)	—
Normalized meal bolus size (unitless)[a]	0.96 (0.94, 0.97)	0.96 (0.95, 0.97)	1.24 (1.22, 1.26)	—
Cumulative basal insulin delivery at 4 h (% of open-loop basal)	103% (77%, 154%)	118% (72%, 147%)	80% (53%, 110%)	204% (173%, 251%)
Cumulative basal plus bolus insulin delivery at 4 h (U)[b]	10.4 (7.8, 13.3)	11.5 (9.7, 13.8)	11.9 (9.3, 14.6)	8.8 (7.3, 11.1)
Glycemic outcomes				
Metrics at start of meal				
Baseline glucose[c]	124 (98, 174)	148 (124, 180)	125 (111, 142)	125 (115, 144)
Metrics over 4 h				
Number of YSI measurements	11 (11, 11)	11 (11, 11)	11 (11, 11)	11 (11, 11)
% of meals with a YSI value				
≤ 60 mg/dL	0	1 (3%)	2 (5%)	0
≤ 70 mg/dL	2 (4%)	3 (8%)	2 (5%)	0
> 180 mg/dL	43 (84%)	35 (88%)	31 (78%)	44 (96%)
> 250 mg/dL	28 (55%)	20 (50%)	10 (25%)	37 (80%)
> 300 mg/dL	15 (29%)	12 (30%)	5 (13%)	19 (41%)
> 400 mg/dL	1 (2%)	0	2 (5%)	0
% of YSI values				
≤ 70 mg/dL	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)
71–180 mg/dL	27% (9%, 64%)	27% (10%, 55%)	55% (30%, 85%)	18% (9%, 27%)
> 180 mg/dL	73% (36%, 91%)	73% (43%, 90%)	41% (9%, 70%)	82% (73%, 91%)
Mean glucose (mg/dL)	204 (159, 249)	203 (164, 250)	168 (150, 205)	231 (208, 245)
Glucose CV	22% (15%, 25%)	21% (16%, 25%)	18% (15%, 26%)	21% (17%, 25%)
Nadir (mg/dL)	124 (98, 167)	133 (97, 176)	114 (101, 138)	139 (121, 151)
Peak (mg/dL)	261 (206, 319)	250 (217, 307)	220 (182, 249)	287 (263, 313)
Excursion (peak minus baseline)[c]	121 (70, 171)	105 (60, 130)	102 (67, 134)	156 (123, 180)
Area under the curve 180 (mg/dL/min)[d]	34 (6, 69)	29 (9, 72)	13 (0, 29)	56 (37, 70)
% meals with a Hypoglycemia red light	9 (18%)	5 (13%)	8 (20%)	3 (7%)
Hypoglycemic treatment interventions[e]	0	1 (3%)	1 (3%)	0
Hyperglycemic treatment interventions[e]	1 (2%)	0	2 (5%)	0
Metrics at 4 h				
Glucose at 4 h	175 (134, 213)	174 (138, 205)	143 (109, 174)	201 (161, 226)
% of meals with a YSI value at 4 h				
≤ 60 mg/dL	0	0	1 (3%)	0
≤ 70 mg/dL	0	0	1 (3%)	0
71–180 mg/dL	27 (53%)	22 (55%)	31 (78%)	16 (35%)
> 180 mg/dL	24 (47%)	18 (45%)	8 (20%)	30 (65%)
> 250 mg/dL	5 (10%)	4 (10%)	2 (5%)	5 (11%)
> 300 mg/dL	2 (4%)	0	2 (5%)	1 (2%)
> 400 mg/dL	0	0	0	0

Data are median (25^{th}, 75^{th} percentiles) values or *n* (%) as indicated.

[a]$Bolus_{NORM} = (bolus_{ACTUAL} \times carbohydrate\ ratio)/meal\ size$.

[b]Includes the meal boluses, correction boluses, and insulin delivered by the controller.

[c]Eleven baseline YSI values and excursions were missing (three with standard bolus delivered with meal, two with standard bolus delivered before meal, three with over-bolus delivered with meal, and three with no bolus delivered with meal).

[d]Area under the curve calculated for each meal and divided by the time.

[e]Hypoglycemic treatments preceded by a red light were not counted as an intervention, and YSI values were not imputed.

CHO, carbohydrate; CV, coefficient of variation.

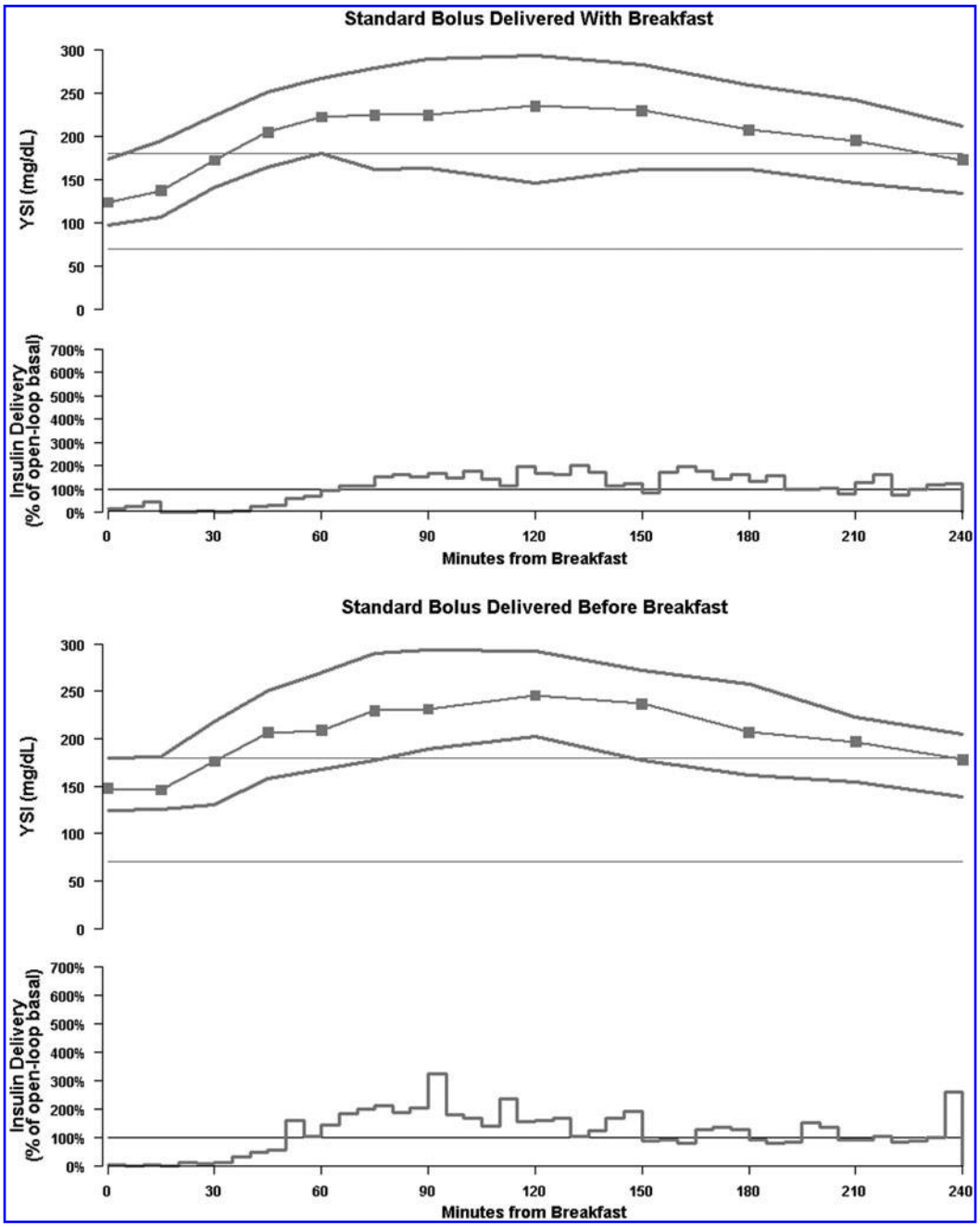

FIG. 1. Glycemic control following standard bolus delivered with and before breakfast: **(top panel)** glucose levels and **(bottom panel)** insulin delivery following breakfast. Lines with dots denote the median glucose, lines without dots denote the 25th and 75th percentiles for glucose, and bars denote mean insulin delivery.

mean glucose level was 168 mg/dL, the median percentage of glucose values 71–180 mg/dL was 55%, and the median excursion was 102 mg/dL. At 4 h after the meal, 78% of meals had a glucose value in this range. The median of the AUC 180 mg/dL was 13 mg/dL/min. The median cumulative basal plus bolus insulin over the 4 h was 11.9 units.

Omitted bolus at time of breakfast

Following an omitted bolus at the time of breakfast, no meals had a required hypoglycemic or hyperglycemic rescue (Table 1). During the 4 h after a breakfast with an omitted bolus, the glucose level did not rise above 400 mg/dL, the median of each participant's mean glucose level was 231 mg/dL, the median percentage of glucose values 71–180 mg/dL was 18%, and the median excursion was 156 mg/dL. At 4 h after the meal, 35% of meals had a glucose value in this range. The median of the AUC 180 mg/dL was 56 mg/dL/min. The median cumulative basal plus bolus insulin over the 4-h period was 8.8 units.

Discussion

Blood glucose levels following the breakfast meal are often difficult to control, related in part to high levels of counterregulatory hormones, less suppression of endogenous

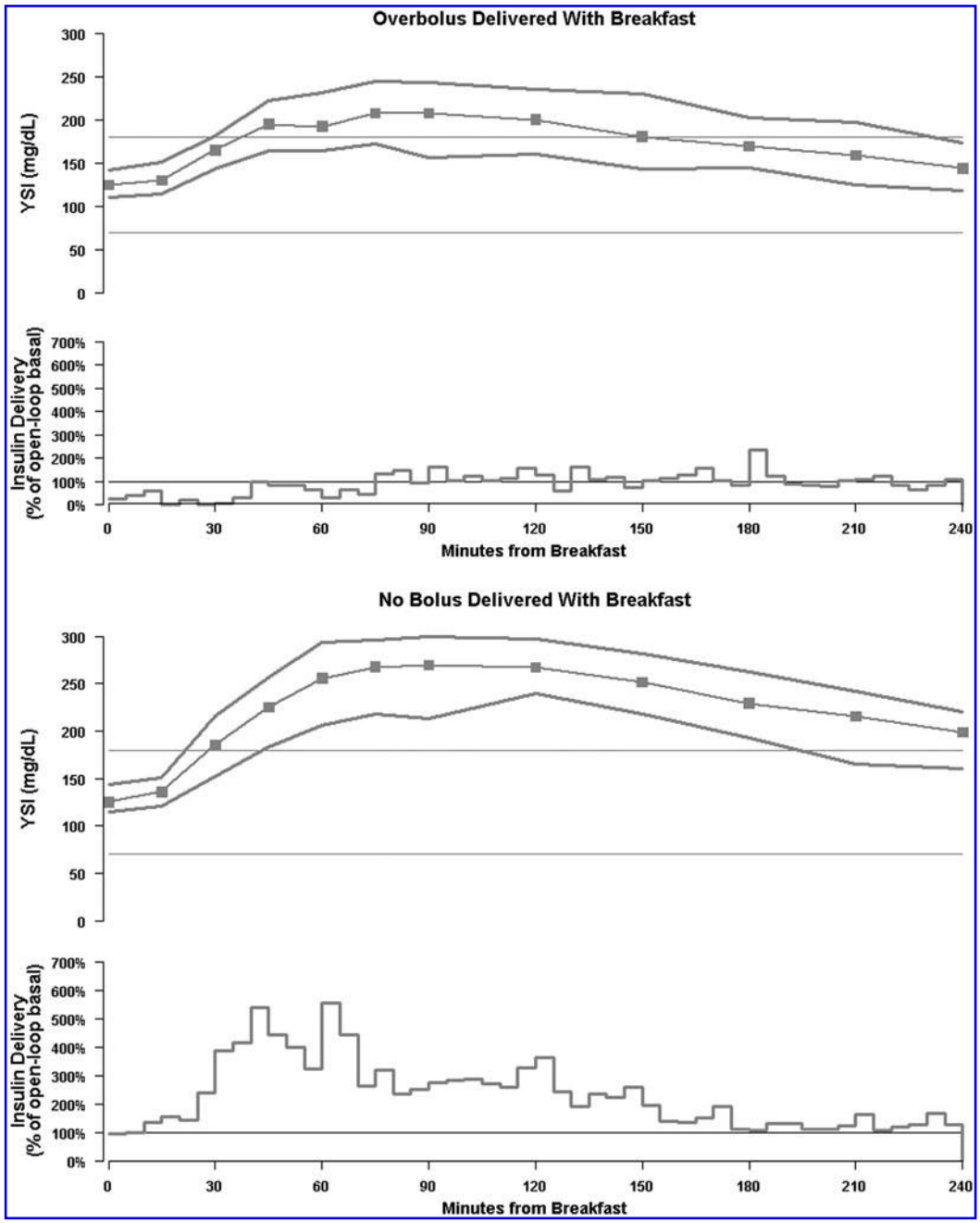

FIG. 2. Glycemic control following over-bolus and no bolus delivered with breakfast: **(top panel)** glucose levels and **(bottom panel)** insulin delivery following breakfast. Lines with dots denote the median glucose, lines without dots denote the 25th and 75th percentiles for glucose, and bars denote mean insulin delivery.

glucose production, lack of optimal I/C ratios, time delay before effect seen for currently available rapid-acting insulin activity, and the high glycemic index of common breakfast foods. We assessed how safely a CL system would function following breakfast under four scenarios: standard bolus given at the time of the breakfast meal (based on the home I/C ratios), standard bolus given 15 min prior to the meal, over-bolus given at the time of the meal, and no bolus given at the time of meal. For all four scenarios, use of the system generally was safe, and no adverse events occurred. Among the 177 breakfasts, external treatment was given for hypoglycemia in one participant when a standard bolus was given 15 min prior to the meal and for one subject following an over-bolus. External treatment for hyperglycemia was given in one participant following a standard bolus given at mealtime and for two participants following an over-bolus. However, except for the over-bolus scenario, glucose levels for most participants were elevated for a substantial portion of the 4 h following breakfast. Although the current study was not powered to compare the breakfast scenarios, the mean glucose level was 15.9 mg/dL lower following a bolus 15 min before the meal compared with a bolus at the same time as the meal, after

controlling for baseline glucose level. Results generally were similar for adults and adolescents (Supplementary Table S3).

The controller used in this safety study had an intentionally conservative design with respect to insulin dosing in the postprandial period. As shown in Figure 1, there generally was a significant reduction of insulin delivery for a period of 30–60 min following the meal bolus, and the insulin delivery for the remainder of the 4-h period was somewhat higher than the subject's standard open-loop basal therapy. The controller's conservative design made it successful in minimizing postprandial hypoglycemia but at the expense of having elevated glucose levels in most subjects. The starting glucose values in the over-bolus and missed-bolus challenges (Fig. 2) were tighter than those in the standard-bolus challenges (Fig. 1). This may have been because the challenges in Figure 2 followed an overnight period of CL control that brought most subjects into a tight range. In contrast, the challenges in Figure 1 were performed after a night of home glucose control.

The finding that glycemic control was better following what was considered to be an over-bolus rather than following a standard bolus was surprising. Although these subjects were in above average glycemic control with a mean hemoglobin A1c level of 7.9%, it is unlikely that their I/C ratios were optimally adjusted. When comparing the 30% over-bolus with the standard meal, the median percentage of postprandial glucose levels in-range increased from 27% to 55% with the over-bolus. Only two of the 40 meals with an over-bolus resulted in subsequent glucose levels below 60 mg/dL (<3.9 mmol/L). This was in part due to the reduction in basal insulin delivery by the controller with the over-bolus, but was likely also related to inadequate standard meal bolus insulin dosages as used in the home setting. CGM values were typically lower than YSI values, making the controller deliver slightly less-than-optimal amounts of insulin, which could partially explain why over-bolus performed better than the standard bolus. This strategy of augmenting the meal bolus and reducing the basal rate over the ensuing 2–4 h is referred to as a ''super bolus'' and is a strategy recommended by Certified Diabetes Educators and used by sophisticated insulin pumpers to reduce postprandial highs, especially when trying to cover high glycemic index foods. Although regular postmeal blood glucose checks for all three meals of the day are recommended by most diabetes care providers, this is rarely done. For optimal postprandial control, trend readings from a CGM and advanced pumping techniques are helpful.[9,23] A CL system that can accomplish this automatically is highly desirable and is needed to help attain optimal postprandial glucose control.

The AP system handled the missed meal bolus safely in relation to hypoglycemia. The median percentage of CL dosing doubled from 103% (standard meal) to 204% (missed meal bolus). Although the percentage of glucose values above 180 mg/dL (>10 mmol/L) increased, there were no YSI glucose values <70 mg/dL (<3.9 mmol/L). There had been a concern that with the high postprandial glucose values secondary to the missed insulin bolus, excessive insulin would be delivered, resulting in postmeal hypoglycemia. However, a safety tuning of the control action prevented this from occurring.

In a previous randomized crossover pilot study of the CL versus the open-loop systems, two versions of the currently used control-to-range algorithm were used to document feasibility and safety,[16] which led to the selection of the algorithm used in the current study. This is the first large study involving different age groups to evaluate the four bolus situations likely to occur in real life. The differences with respect to previous results reported in the above-mentioned study[16] highlight the fact that a multicenter intercontinental trial with adults and adolescents and with a more realistic protocol that includes meal over-/under-boluses is much more challenging than a small study in a single center. Comparison with other published trials performed in one or a few centers with very rigid protocols is also difficult, for the same reasons.

Initial studies of the AP have often focused on overnight glucose control rather than postprandial glucose levels.[24,25] Several groups have recently reported studies of CL management that included meal boluses.[7,26–28] In the only study comparable in size to the present study, 47 adults were studied during three 23-h admissions for comparison of two CL algorithms with open-loop management.[5] Although time spent <3.9 mmol/L (70 mg/dL) was significantly reduced with both CL systems, mean glucose levels were higher, as were blood glucose levels postprandially, in comparison with open-loop management.

Although not used in the current report, several groups have demonstrated use of a bihormonal CL AP system to administer larger meal insulin boluses with the availability of small doses of glucagon to prevent later hypoglycemia.[4,6,8] As only one subject in our 91 standard and premeal bolus experiments had a postprandial glucose value <60 mg/dL, glucagon administration would not appear indicated in the current CL system. However, this would likely change if the current algorithm was altered to allow larger meal insulin boluses.

A limitation of the current study is that the breakfast bolus studies were not randomized. The prebolus study was conducted first, followed by the missed bolus, the standard bolus, and then the over-bolus study. A possible reason for the ''chance'' elevation of the fasting glucose levels in the prebolus study might have been related to the stress of having been the first study. Other limitations include the need to evaluate the system in real-life outpatient situations, which include factors such as exercise, various types of meals (e.g., high fat), and stress. Insulin levels were not measured and potentially could provide information to support the glucodynamic metrics. The use of the subjects' home I/C ratios likely resulted in suboptimal bolus dosages for many subjects. Previous studies using a control algorithm for 2 weeks showed postmeal glucose levels to be optimally controlled.[9,23] However, it is likely that AP systems will need to deal with suboptimal glycemic control in real-life usage. Additionally, subjects were served precise amounts of CHO, and their home I/C ratios were applied to this precisely measured CHO amount. However, subjects may systematically over- or underestimate CHO intake at home, resulting in I/C ratios that are skewed to compensate for the subject's errors. Allowing the subject to estimate the CHO amount in the meal may have resulted in a more realistic dosing of the meal bolus.

The American Diabetes Association goal to have all glucose levels below 180 mg/dL following a meal was not met for over 75% of the four bolus studies. This goal is unlikely to be reached with complete CL glucose control until a more rapid-acting insulin becomes available. Likely, some degree

of meal announcement will be required for any current CL system. The use of pramlintide in a CL system to delay food absorption and reduce postprandial glucagon levels delayed the time from meal start to peak plasma glucose.[29] However, pramlintide failed to reduce the magnitude of the rise in glucose levels after breakfast.[29] Clearly, further research is needed if the American Diabetes Association goal for postprandial glucose levels is to be met in subjects using a CL system. Finally, these data provide an important opportunity to test the validity of the University of Virginia/Padova type 1 diabetes simulator[30] in postprandial conditions in both adolescents and adults. This can be easily achieved with a procedure similar to that previously described.[31]

In summary, this large multicenter inpatient study showed the CL system handled the four bolus situations safely. As a result, outpatient studies using this controller are underway.[29] In order to more effectively handle postprandial glucose levels, further modifications of the algorithm have been introduced.[32,33] Some promising results have been obtained in a small clinical trial.[34] The improved controller will be tested soon in a larger trial.

The continued development of CL algorithms and the portability of the systems will be important. As these features continue to be developed, optimal glycemic control will hopefully become a reality for many more people with T1D.

Acknowledgments

We would like to recognize the efforts of the participants and their families and thank them. The project described was supported by grant 22-2011-643 from the JDRF. Continuous glucose monitors and sensors were purchased at a bulk discount price from Insulet Corp. (Bedford, MA) and Dexcom (San Diego, CA). Home glucose meters and test strips were provided to the study by Abbott Diabetes Care, Inc. The companies had no involvement in the design, conduct, or analysis of the trial or the manuscript preparation.

Author Disclosure Statement

The study was designed and conducted by the investigators. The writing group collectively wrote the manuscript and vouch for the data. H.P.C. is the guarantor of this work and, as such, had full access to all the data in the study and is responsible for the integrity of the data and the accuracy of the data analysis. H.P.C., F.J.D. III, H.Z., E.R., R.N., C.C., B.A.B., D.M.M., and S.A. researched data, contributed to the discussion, and reviewed/edited the manuscript. L.M., J.L., P.C., C.K., and R.W.B. contributed to the discussion and reviewed/edited the manuscript.

H.P.C. reports grants from Dexcom outside of the submitted work. H.Z. reports grants, personal fees, and nonfinancial support from Insulet, grants and nonfinancial support from LifeScan, and grants from Dexcom during the conduct of the study, as well as grants, personal fees, and nonfinancial support from Animas, grants and personal fees from Roche, personal fees from Cellnovo, personal fees from MannKind, grants and nonfinancial support from Abbott, grants and nonfinancial support from Eli Lilly, grants and nonfinancial support from GluMetrics, grants and nonfinancial support from Medtronic, grants and nonfinancial support from Novo Nordisk, and grants and nonfinancial support from Sanofi outside of the submitted work. E.R. reports personal fees from A. Menarini Diagnostics, personal fees and nonfinancial support from Abbott Diabetes Care, personal fees from Cellnovo, personal fees and nonfinancial support from Dexcom, personal fees from Eli Lilly, personal fees from Animas, personal fees from Medtronic, personal fees from Novo Nordisk, personal fees and nonfinancial support from Roche Diagnostics, personal fees from Sanofi-Aventis, nonfinancial support from Insulet, and personal fees from LifeScan outside of the submitted work. B.A.B. reports grants from the JDRF during the conduct of the study, as well as grants, personal fees, and nonfinancial support from Medtronic Diabetes, nonfinancial support from Dexcom, personal fees from BD, personal fees from Sanofi-Aventis, personal fees from Roche, and personal fees from Glysense outside of the submitted work. In addition, B.A.B. has a U.S. patent issued for ''Method and Apparatus for Real-Time Control of Glucose'' (number 60/234,632), and B.A.B. and H.P.C. have a pending U.S. patent application ''Predictive Low Glucose Suspend'' (number 61/197,230). S.A. reports grants from the JDRF during the conduct of the study and grants from Animas, Inc., Medtronic Diabetes, Inc., and Senseonics, Inc., outside the submitted work. L.M. reports grants from the Italian MIUR during the conduct of the study. C.K. and R.W.B. reports grants from the JDRF during the conduct of the study. F.J.D. III, R.N., C.C., D.M.M., J.L., and P.C. declare no competing financial interests exist.

Appendix

Clinical Centers

Listed with clinical center name, city, and state. Personnel are listed as (PI) for Principal Investigator, (I) for co-Investigator, (C) for Coordinator, (E) for Engineer, (B) for Biostatistician, and (O) for other personnel positions:

Sansum Diabetes Research Institute, Santa Barbara, CA. Howard Zisser, MD (PI); Lois Jovanovic, MD (I); Alison Wollitzer, PhD (I); Wendy Bevier, PhD (I); Eyal Dassau, PhD (I, E); Kristin Castorino, DO (I); Kateryna Markova, MD (C); Jacqueline Wiley, MA (O); Erin Beveridge, BS (O); Nicolas Santibanez, RN (O); Alexandra Sales, BS (O); Maia Bradley, BS (O); Adam Castorino, AS (O).

University of Virginia, Charlottesville, VA. Boris Kovatchev, MD (PI); Stacey Anderson, MD (I); Susan Demartini, MD (I); Sue Brown, MD (I); William Clarke, MD (I); Marc Breton, PhD (I, E); Stephen Patek, PhD (E); Patrick Keith-Hynes, PhD (E); Colleen Hughes-Karvetski, PhD (O); Molly McElwee, RN, CDE (C); Mary Oliveri, CCRC (C); Christian Wakeman, BS (O).

Montpellier University Hospital, Department of Endocrinology, Diabetes, Nutrition and INSERM 1001 Clinical Investigation Center, the Institute of Functional Genomics, UMR CNRS 5203/INSERM U661, University of Montpellier, Montpellier, France. Eric Renard, MD, PhD (PI); Anne Farret, MD, PhD (I); Marie-Josee Pelletier, MD (I); Hugues Chevassus, PharmD (O); Jerome Place, MSc (E, C).

Jesse Z. and Sara Lea Shafer Institute for Endocrinology and Diabetes, National Center for Childhood Diabetes, Schneider

Children's Medical Center of Israel and Sackler Faculty of Medicine, Tel-Aviv University, Tel Aviv, Israel. Moshe Phillip, MD (PI); Eran Atlas, MSc (I); Revital Nimri, MD (I); Tal Oron, MD (I); Alon Farfel, MD (I); Sharon Demol, MD (I); Eran Mel, MD (I); Tal Ben-Ari, MD (I), Michael Gilon, PhD (I); Ayele Parnes (C); Ido Muller, BSc (C); Shahar Miller, BSc (C); Alona Hamou, MSc (O); Orna Hermon, BSc (O); Galit Shiovitch-Mantzuri, RN (O); Galia Fayman, BSc (O).

University of Padova, Padova, Italy. Claudio Cobelli, Ph.D. (PI); Chiara Dalla Man, Ph.D. (I); Angelo Avogaro, M.D., Ph.D. (I); Daniela Bruttomesso, M.D., Ph.D (I); Alberto Maran, M.D. (C); Michele Schiavon (O); Simone Del Favero, Ph.D. (E,C); Roberto Vistenin, M.Sc (O), Rachele Scotton, M.D. (O); Alessio Filippi, M.D. (O).

University of Pavia, Pavia, Italy. Lalo Magni, PhD (PI); Chiara Toffanin, PhD (I, E); Giuseppe De Nicolao, PhD (E); Simone Mancini, BSc (O); Davide Martino Raimondo, PhD (E).

Division of Pediatric Endocrinology and Diabetes, Stanford University, Stanford, CA: Bruce Buckingham, MD (PI); Darrell M. Wilson, MD (I); Kari Benassi, NP (C); Paula Clinton, RN, CDE (C); Breanne P. Harris, BS (C); Satya Shanmugham, BS (O), Kimberly Caswell, RN, CDE (O).

Barbara Davis Center for Childhood Diabetes, University of Colorado, Aurora, CO: H. Peter Chase, MD (PI); David M. Maahs, MD, PhD (I); Robert Slover, MD (I); Sally Sullivan, BSN, CDE (C); Laurel Messer, RN, CDE (C); Victoria Gage, BSN, CDE (C); Jaime Realsen, BS (C); Emily Westfall, BA, BS (O); Hannah Goettle, BS (O).

Department of Chemical Engineering, University of California, Santa Barbara, Santa Barbara, CA: Francis J. Doyle III, Ph.D (PI).

Coordinating Center

Jaeb Center for Health Research, Tampa, FL: Roy W. Beck, MD, PhD (PI); John Lum, MS (I); Craig Kollman, PhD (B); Peter Calhoun, MA (B); Judy Sibayan, MPH (C); Nelly M. Njeru (C); Werner Sauer (E).

Data and Safety Monitoring Board

John C. Pickup, BM, DPhil (chair); Irl Hirsch, MD; Howard Wolpert, MD.

References

1. Standards of medical care in diabetes—2013. Diabetes Care 2013;36(Suppl 1):S11–S66.
2. Cobry E, McFann K, Messer L, Gage V, VanderWel B, Horton L, Chase HP: Timing of meal insulin boluses to achieve optimal postprandial glycemic control in patients with type 1 diabetes. Diabetes Technol Ther 2010;12:173–177.
3. Luijf YM, van Bon AC, Hoekstra JB, Devries JH: Premeal injection of rapid-acting insulin reduces postprandial glycemic excursions in type 1 diabetes. Diabetes Care 2010; 33:2152–2155.
4. Castle JR, Engle JM, El Youssef J, Massoud RG, Yuen KC, Kagan R, Ward WK: Novel use of glucagon in a closed-loop system for prevention of hypoglycemia in type 1 diabetes. Diabetes Care 2010;33:1282–1287.
5. Luijf YM, DeVries JH, Zwinderman K, Leelarathna L, Nodale M, Caldwell K, Kumareswaran K, Elleri D, Allen JM, Wilinska ME, Evans ML, Hovorka R, Doll W, Ellmerer M, Mader JK, Renard E, Place J, Farret A, Cobelli C, Del Favero S, Dalla Man C, Avogaro A, Bruttomesso D, Filippi A, Scotton R, Magni L, Lanzola G, Di Palma F, Soru P, Toffanin C, De Nicolao G, Arnolds S, Benesch C, Heinemann L: Day and night closed-loop control in adults with type 1 diabetes: a comparison of two closed-loop algorithms driving continuous subcutaneous insulin infusion versus patient self-management. Diabetes Care 2013;36: 3882–3887.
6. Russell SJ, El-Khatib FH, Nathan DM, Magyar KL, Jiang J, Damiano ER: Blood glucose control in type 1 diabetes with a bihormonal bionic endocrine pancreas. Diabetes Care 2012;35:2148–2155.
7. Weinzimer SA, Steil GM, Swan KL, Dziura J, Kurtz N, Tamborlane WV: Fully automated closed-loop insulin delivery versus semiautomated hybrid control in pediatric patients with type 1 diabetes using an artificial pancreas. Diabetes Care 2008;31:934–939.
8. El-Khatib FH, Russell SJ, Nathan DM, Sutherlin RG, Damiano ER: A bihormonal closed-loop artificial pancreas for type 1 diabetes. Sci Transl Med 2010;2:27ra27.
9. Zisser H, Jovanovic L, Doyle F 3rd, Ospina P, Owens C: Run-to-run control of meal-related insulin dosing. Diabetes Technol Ther 2005;7:48–57.
10. Rutledge KS, Chase HP, Klingensmith GJ, Walravens PA, Slover RH, Garg SK: Effectiveness of postprandial Humalog in toddlers with diabetes. Pediatrics 1997;100:968–972.
11. Burdick J, Chase HP, Slover RH, Knievel K, Scrimgeour L, Maniatis AK, Klingensmith GJ: Missed insulin meal boluses and elevated hemoglobin A1c levels in children receiving insulin pump therapy. Pediatrics 2004;113:e221–e224.
12. Olinder AL, Kernell A, Smide B: Missed bolus doses: devastating for metabolic control in CSII-treated adolescents with type 1 diabetes. Pediatr Diabetes 2009;10:142–148.
13. Vanderwel BW, Messer LH, Horton LA, McNair B, Cobry EC, McFann KK, Chase HP: Missed insulin boluses for snacks in youth with type 1 diabetes. Diabetes Care 2010; 33:507–508.
14. Kramer CK, Borgono CA, Van Nostrand P, Retnakaran R, Zinman B: Glucagon response to oral glucose challenge in type 1 diabetes: lack of impact of euglycemia. Diabetes Care 2014;37:1076–1082.
15. Rosenstock J, Park G, Zimmerman J; U.S. Insulin Glargine (HOE 901) Type 1 Diabetes Investigator Group: Basal insulin glargine (HOE 901) versus NPH insulin in patients with type 1 diabetes on multiple daily insulin regimens. Diabetes Care 2000;23:1137–1142.
16. Breton M, Farret A, Bruttomesso D, Anderson S, Magni L, Patek S, Dalla Man C, Place J, Demartini S, Del Favero S, Toffanin C, Hughes-Karvetski C, Dassau E, Zisser H, Doyle FJ 3rd, De Nicolao G, Avogaro A, Cobelli C, Renard E, Kovatchev B: Fully integrated artificial pancreas in type 1 diabetes: modular closed-loop glucose control maintains near normoglycemia. Diabetes 2012;61:2230–2237.

17. Cobelli C, Renard E, Kovatchev B: Artificial pancreas: past, present, future. Diabetes 2011;60:2672–2682.
18. Hughes CS, Patek SD, Breton MD, Kovatchev BP: Hypoglycemia prevention via pump attenuation and red-yellow-green ''traffic'' lights using continuous glucose monitoring and insulin pump data. J Diabetes Sci Technol 2010;4:1146–1155.
19. Kovatchev B, Cobelli C, Renard E, Anderson S, Breton M, Patek S, Clarke W, Bruttomesso D, Maran A, Costa S, Avogaro A, Dalla Man C, Facchinetti A, Magni L, De Nicolao G, Place J, Farret A: Multinational study of subcutaneous model-predictive closed-loop control in type 1 diabetes mellitus: summary of the results. J Diabetes Sci Technol 2010;4:1374–1381.
20. Kovatchev B, Patek S, Dassau E, Doyle FJ III, Magni L, De Nicolao G, Cobelli C; Juvenile Diabetes Research Foundation Artificial Pancreas Consortium: Control to range for diabetes: functionality and modular architecture. J Diabetes Sci Technol 2009;3:1058–1065.
21. Magni L, Raimondo DM, Bossi L, Dalla Man C, De Nicolao G, Kovatchev B, Cobelli C: Model predictive control of type 1 diabetes: an in silico trial. J Diabetes Sci Technol 2007;1:804–812.
22. Patek SD, Magni L, Dassau E, Karvetski C, Toffanin C, De Nicolao G, Del Favero S, Breton M, Man CD, Renard E, Zisser H, Doyle FJ 3rd, Cobelli C, Kovatchev BP: Modular closed-loop control of diabetes. IEEE Trans Biomed Eng 2012;59:2986–2999.
23. Zisser H, Palerm CC, Bevier WC, Doyle FJ 3rd, Jovanovic L: Clinical update on optimal prandial insulin dosing using a refined run-to-run control algorithm. J Diabetes Sci Technol 2009;3:487–491.
24. O'Grady MJ, Retterath AJ, Keenan DB, Kurtz N, Cantwell M, Spital G, Kremliovsky MN, Roy A, Davis EA, Jones TW, Ly TT: The use of an automated, portable glucose control system for overnight glucose control in adolescents and young adults with type 1 diabetes. Diabetes Care 2012;35:2182–2187.
25. Phillip M, Battelino T, Atlas E, Kordonouri O, Bratina N, Miller S, Biester T, Stefanija MA, Muller I, Nimri R, Danne T: Nocturnal glucose control with an artificial pancreas at a diabetes camp. N Engl J Med 2013;368:824–833.
26. Dauber A, Corcia L, Safer J, Agus MS, Einis S, Steil GM: Closed-loop insulin therapy improves glycemic control in children aged <7 years: a randomized controlled trial. Diabetes Care 2013;36:222–227.
27. Elleri D, Allen JM, Biagioni M, Kumareswaran K, Leelarathna L, Caldwell K, Nodale M, Wilinska ME, Acerini CL, Dunger DB, Hovorka R: Evaluation of a portable ambulatory prototype for automated overnight closed-loop insulin delivery in young people with type 1 diabetes. Pediatr Diabetes 2012;13:449–453.
28. Mauseth R, Hirsch IB, Bollyky J, Kircher R, Matheson D, Sanda S, Greenbaum C: Use of a ''fuzzy logic'' controller in a closed-loop artificial pancreas. Diabetes Technol Ther 2013;15:628–633.
29. Weinzimer SA, Sherr JL, Cengiz E, Kim G, Ruiz JL, Carria L, Voskanyan G, Roy A, Tamborlane WV: Effect of pramlintide on prandial glycemic excursions during closed-loop control in adolescents and young adults with type 1 diabetes. Diabetes Care 2012;35:1994–1999.
30. Dalla Man C, Micheletto F, Lv D, Breton M, Kovatchev B, Cobelli C: The UVA/PADOVA type 1 diabetes simulator: new features. J Diabetes Sci Technol 2014;8:26–34.
31. Visentin R, Dalla Man C, Kovatchev B, Cobelli C: The University of Virginia/Padova type 1 diabetes simulator matches the glucose traces of a clinical trial. Diabetes Technol Ther 2014;16:428–434.
32. Soru P, De Nicolao G, Toffanin C, Dalla Man C, Cobelli C, Magni L; AP@home Consortium: MPC based artificial pancreas: strategies for individualization and meal compensation. Annu Rev Control 2012;36:118–128.
33. Toffanin C, Messori M, Di Palma F, De Nicolao G, Cobelli C, Magni L: Artificial pancreas: model predictive control design from clinical experience. J Diabetes Sci Technol 2013;7:1470–1483.
34. Del Favero S, Bruttomesso D, Di Palma F, Lanzola G, Visentin R, Filippi A, Scotton R, Toffanin C, Messori M, Scarpellini S, Keith-Hynes P, Kovatchev BP, Devries JH, Renard E, Magni L, Avogaro A, Cobelli C; AP@home Consortium: First use of model predictive control in outpatient wearable artificial pancreas. Diabetes Care 2014;37:1212–1215.

Address correspondence to:
Roy W. Beck, MD, PhD
Jaeb Center for Health Research, Inc.
15310 Amberly Drive, #350
Tampa, FL 33647

E-mail: rbeck@jaeb.org