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ORIGINAL ARTICLE

Design and Clinical Evaluation of a Novel Low-Glucose Prediction Algorithm with Mini-Dose Stable Glucagon Delivery in Post-Bariatric Hypoglycemia

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Abstract

Background: Postbariatric hypoglycemia (PBH) is a complication of bariatric surgery with limited therapeutic options. We developed an event-based system to predict and detect hypoglycemia based on continuous glucose monitor (CGM) data and recommend delivery of minidose liquid glucagon.

Methods: We performed an iterative development clinical study employing a novel glucagon delivery system: a Dexcom CGM connected to a Windows tablet running a hypoglycemia prediction algorithm and an Omnipod pump filled with an investigational stable liquid glucagon formulation. Meal tolerance testing was performed in seven participants with PBH and history of neuroglycopenia. Glucagon was administered when hypoglycemia was predicted. Primary outcome measures included the safety and feasibility of this system to predict and prevent severe hypoglycemia. Secondary outcomes included hypoglycemia prediction by the prediction algorithm, minimization of time below hypoglycemia threshold using glucagon, and prevention of rebound hyperglycemia.

Results: The hypoglycemia prediction algorithm alerted for impending hypoglycemia in the postmeal state, prompting delivery of glucagon (150 μg). After observations of initial incomplete efficacy to prevent hypoglycemia in the first two participants, system modifications were implemented: addition of PBH-specific detection algorithm, increased glucagon dose (300 μg), and a second glucagon dose if needed. These modifications, together with rescue carbohydrates provided to some participants, contributed to progressive improvements in glucose time above the hypoglycemia threshold (75 mg/dL).

Conclusions: Preliminary results indicate that our event-based automatic monitoring algorithm successfully predicted likely hypoglycemia. Minidose glucagon therapy was well tolerated, without prolonged or severe hypoglycemia, and without rebound hyperglycemia.

Keywords: Hypoglycemia, Bariatric surgery, Glucagon.

Introduction

BARIATRIC SURGERY RESULTS in sustained weight loss and improvement in weight-related comorbidities, including improved glycemic control in type 2 diabetes.[1–3] One increasingly recognized complication of bariatric surgery is hypoglycemia, occurring most commonly after Roux-en-Y gastric bypass (RYGB) but also reported after vertical sleeve gastrectomy.[4] Up to 75% of patients with prior RYGB have asymptomatic hypoglycemia (<55 mg/dL) measured by continuous glucose monitor (CGM)[5]; severe neuroglycopenia is less frequent (range <1%–10%).[4]

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Postbariatric hypoglycemia (PBH) typically occurs one to three hours after meals, with increased severity after ingestion of high-glycemic index carbohydrates.[6–8] Although the etiology of PBH has not been fully elucidated, excessive postprandial incretin and insulin secretion, reduced insulin clearance,[9] and insulin-independent mechanisms are likely contributors.[8,10–12] Moreover, counter-regulatory hormones, including glucagon,[13] catecholamines, and cortisol, are reduced during experimentally induced hypoglycemia in RYGB patients.[14]

Initial PBH treatment includes medical nutrition therapy, aimed at reduction in high-glycemic index carbohydrates.[15] Pharmacologic interventions are often required. Acarbose minimizes the rapid postprandial rise in glucose and insulin, thereby reducing subsequent hypoglycemia.[16,17] Additional treatments include octreotide to reduce incretin and insulin secretion,[18] diazoxide and/or calcium channel blockers to reduce insulin secretion,[17,19] providing nutrition solely through a gastrostomy tube in the bypassed stomach,[20] or reversal of bypass.[21] CGM may improve safety in patients with hypoglycemic unawareness.[22] Unfortunately, many of these approaches are either poorly tolerated or incompletely effective, even in combination.

Severe hypoglycemia can result in syncope, falls, and seizures, and hypoglycemia can cause cardiac arrhythmias.[23,24] Hypoglycemia occurring multiple times per day can lead to hypoglycemic unawareness, reducing safety in driving and employment, reducing autonomy, and causing fear of eating and activity. Thus, there is an urgent need for improved approaches for treatment of severe hypoglycemia to maintain health, allow optimal nutrition, and improve safety.

Glucagon has been used for hypoglycemia, resulting from excess exogenous insulin in diabetes, tumor-induced hypoglycemia,[25] and neonatal hyperinsulinism.[26] Glucagon can be used for acute treatment of hypoglycemia in PBH; however, several shortcomings of traditional glucagon preparations limit utilization. First, the need for reconstitution of glucagon powder can be daunting for the patient or family members during hypoglycemia. Second, glucagon emergency kits are expensive and must be used within 24 h after reconstitution, limiting each kit to one-time use. Finally, traditional rescue doses (0.5–1.0 mg) can cause nausea and rebound hyperglycemia.[27]

Indeed, in a previous study, we demonstrated that a constant infusion of glucagon increased glucose above baseline, promoting further insulin secretion after a mixed meal and increased severity of subsequent hypoglycemia.[28] A newly developed stable liquid formulation of native glucagon[29] can be delivered through infusion pump, allowing lower ''minidoses'' to be delivered only when hypoglycemia may be imminent.

We hypothesized that real-time detection of hypoglycemia and rapid administration of lower, more physiologic doses of glucagon would be an effective strategy to reduce the likelihood and severity of hypoglycemia in PBH, while preventing rebound hyperglycemia. Thus, we performed an iterative design-and-evaluation study to assess the performance of a novel event-based hypoglycemia prediction algorithm that triggers manual delivery of minidose glucagon through a patch pump.

Materials and Methods

Clinical

Participants. Participants with a history of RYGB surgery and PBH with neuroglycopenia, uncontrolled on medical nutrition therapy and medications, were recruited from the hypoglycemia clinic. Exclusion criteria included fasting hypoglycemia, known insulinoma, major systemic illness, pregnancy, substance or alcohol abuse, recent steroid or investigational drug exposure, and use of medications (beyond hypoglycemia treatment) known to affect insulin secretion or action. The Joslin Diabetes Center Committee on Human Studies approved the study. Written informed consent was obtained from all participants.

Initiation of glucagon delivery system and mixed meal tolerance testing. Two Dexcom G4 (505-algorithm) CGMs were blinded and then inserted into the anterior abdominal wall; participants were instructed to perform calibrations when prompted. Participants were asked to return 48 to 72 h later, after an overnight fast. Medications, including acarbose, short-acting octreotide, and diazoxide, were held for at least 24 h before the study visit. After intravenous catheter placement for blood sampling, a subcutaneous Omnipod pump (Insulet Corporation, Billerica, MA) filled with investigational glucagon (Xeris Pharmaceuticals, Austin, TX) was inserted into the anterior abdominal wall. After calibration of both CGMs, the sensor with glucose values most closely matching the serum glucose was connected to the Windows tablet running the portable Artificial Pancreas System[30] (pAPS) and the PBH detection algorithm.

After baseline blood sampling, a liquid mixed meal (two bottles of Ensure Compact, containing 64 g carbohydrate, 18 g protein, 12 g fat, 440 kcal, 236 mL volume) was consumed over 5 min. This high-carbohydrate meal was chosen as an experimental intervention to increase the likelihood that participants would have a postprandial glucose and insulin surge, leading to subsequent rapid drop in glucose, and if untreated, hypoglycemia in a pattern characteristic of PBH. Induction of this pattern of postprandial glycemia was necessary to test the capacity of the CGM-informed glucagon delivery system to detect and respond to patterns of hypoglycemia in PBH.

Sensor and plasma glucose, insulin, C-peptide, and glucagon concentrations were measured at baseline and at predetermined intervals after the mixed meal and for 2 h after glucagon delivery. Insulin and C-peptide levels were not available for the final participant due to technical assay issues.

The hypoglycemia threshold parameter was selected conservatively as 75 mg/dL (chosen to account for possible sensor lag with respect to reference glucose and to ensure safety during clinical studies). When the system predicted impending glucose levels lower than the threshold, an alert was generated in two ways: (1) an audible alarm was emitted from the pAPS device and (2) a text message (SMS) was sent to the study physicians and technical team. Upon receipt of the alert, a venous blood sample was obtained. The study physician then activated the Omnipod pump to deliver a dose of investigational glucagon. For the first five studies (stages A and B), participants received 150 μg of glucagon over 2.25 min. The next three participants (6–8, stage C) received 300 μg glucagon over 4.5 min. The protocol employed for the final participant (stage D) included a 300 μg dose, followed by a 150 μg dose for a second impending hypoglycemia alert, or a 300 μg dose if sensor glucose was <75 mg/dL.

For all participants, the pump was removed 30 min after final glucagon delivery. After 2 h, a standard low-carbohydrate

lunch was provided, and participants were observed for two additional hours before discharge. Differences in study protocol across the four sequential stages of the study are summarized in Figure 1.

Investigational glucagon formulation. Glucagon[31] (Xeris Pharmaceuticals) was provided in vials as a premixed nonaqueous liquid stored at room temperature. Samples from glucagon vials were analyzed to determine glucagon concentration using high-performance liquid chromatography (HPLC; Integrity Bio, Inc., Camarillo, CA).

Hypoglycemia scale. The Edinburgh Hypoglycemia Scale was used to assess hypoglycemia symptoms[32] at baseline, at time of hypoglycemia prediction alarm, and 15, 30, and 60 min after glucagon bolus. This scale includes 5 autonomic, 8 neuroglycopenic, 5 nonspecific, and 10 unrelated (dummy) symptoms. Scores for the 5 autonomic, 8 neuroglycopenic, and 5 nonspecific symptoms were summed for each time point.

Hormonal analyses. Plasma glucose was measured by glucose oxidation (YSI 2300 STAT, Yellow Springs, OH), and insulin and C-peptide were measured by electrochemiluminesence (Roche Diagnostics; Celerion, Lincoln, NE). Using solid phase extraction, plasma glucagon was quantified using LC-MS/MS with weighted quadratic regression analysis of peak area ratios of the analyte and internal standard (Celerion).

Statistics. As an algorithm iterative development study, sample size was not determined by a power calculation. Statistical analyses were performed using GraphPad Prism (GraphPad Software, La Jolla, CA). Normally distributed data are expressed as mean ± standard deviation and skewed data are expressed as median with interquartile range. Normality was determined using the Shapiro–Wilk test.[33] Statistical significance was determined with the Wilcoxon signed-rank test.[34]

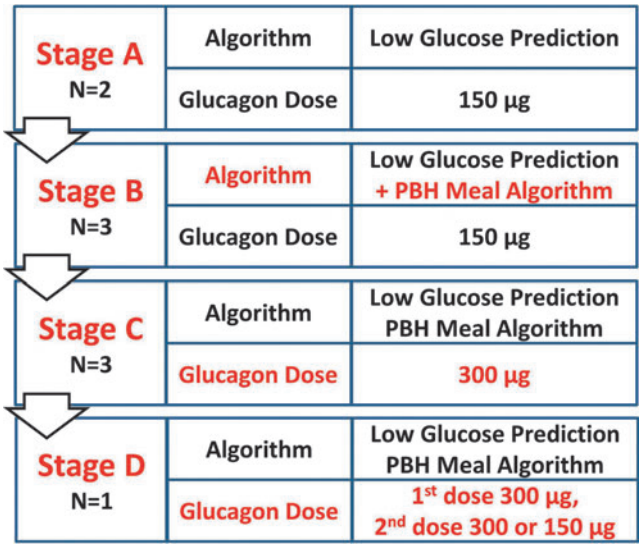

FIG. 1. Stages of system development. Updated characteristics are highlighted in red for each stage.

Algorithm development

Hypoglycemia prediction algorithm development. We implemented the PBH Detection System (PBH-DS) in the pAPS,[30] a computer interface running in a Windows 7 tablet with WiFi connectivity. The software functions to (1) register and store all values from the CGM sensor, (2) provide values to the PBH-DS, and (3) communicate impending hypoglycemia to the clinical team.

The PBH-DS was designed and fine tuned over the course of this study, with the objective of developing an algorithm designed specifically for patients with PBH. The underlying mechanism of hypoglycemia prediction is based on the Low Glucose Predictor (LGP) algorithm,[35] which was validated in patients with type 1 diabetes.[36–38] Two different versions were implemented: *PBH-DSv001* was used in stage A and *PBH-DSv002* was used in stages B, C, and D.

PBH-DSv001. The first version of PBH-DS was an updated version of LGP[35] with modified parameters that were tuned to better cope with the glucose dynamics of PBH. Values for parameters (nomenclature maintained from the original LGP source[35]) were fixed to the following: $\Delta G = 3$ mg/dL/min is the maximum allowed difference between consecutive CGM samples by the noise-spike filtering module; $\tau_F = 3$ min is the time constant of the low-pass filter, $\#al = 1$ is the number of consecutive alarms necessary to issue a hypoglycemia alert, $th = 75$ mg/dL is the hypoglycemia threshold, $ph = 15$ min is the prediction horizon for hypoglycemia, $G_{MAX} = 100$ mg/dL is the glucose threshold beyond which the algorithm will not issue alarms, and $G'_{MAX} = -0.5$ mg/dL/min and $G'_{MIN} = -3$ mg/dL/min are the maximum and minimum values of the glucose rate of change (ROC) for the detection algorithm to be active.

PBH-DSv002. The second version of PBH-DS is composed of two modules working simultaneously, offering redundancy to provide additional safety. The first (and novel) module implements the PBH alarm, which is designed to detect impending hypoglycemia up to 30 min before it occurs, and is executed only after a meal has been consumed and detected. This module was tuned to fit the expected high ROC in PBH. The second module is the LGP* alarm (similar to that implemented in *PBH-DSv001*, but with different parameter values), which detects impending hypoglycemia, with or without preceding meal ingestion. The structure of the detection system is summarized in Figure 2.

The combination of PBH and LGP* alarms allows for a much faster warning to the clinical team in the case of a rapid descent of glucose after a meal, while still maintaining the detection strengths of the original LGP algorithm. The algorithm implements a safety ''lockout'' mechanism that prevents issuing an alarm if a hypoglycemia alert had been issued recently (30 min, or 15 min if glucose <60 mg/dL).

PBH alarm. Glycemic patterns after a mixed meal are characterized by an initial postprandial peak, followed by a very rapid drop in glucose. This provides little time for the PBH-DS to react before hypoglycemia occurs. These patterns inspired the design of a meal detection routine (described below) that changes the algorithm mode if a meal has been recently detected. The routine, which is called after every sensor glucose sample, works by analyzing CGM history

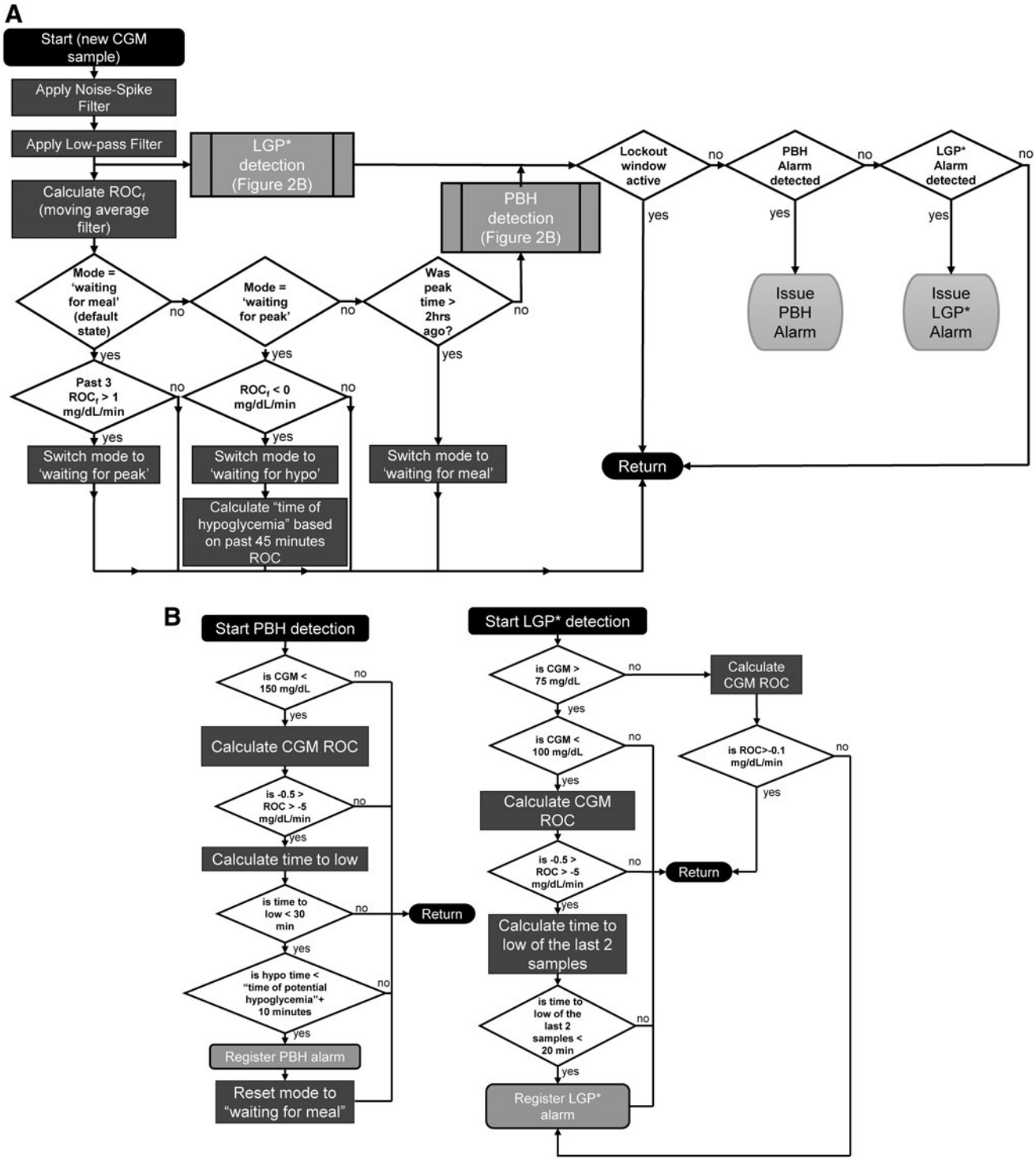

FIG. 2. **(A)** Flowchart of the *PBH-DSv002*. After acquisition of each new CGM sensor glucose value, the logic here described is followed, which results in either issuance of an alarm or return to standby. **(B)** Blocks of PBH and LGP* alarm systems. Secondary flowcharts for the two processes for hypoglycemia detection implemented in the PBH-DS, corresponding to the nested boxes in **(A)**. Left chart describes the logic flow after meal detection (PBH detection). Right chart describes the logic flow if CGM sensor signal approaches the hypoglycemia threshold, even if no meal had been detected. CGM, continuous glucose monitor; LGP, Low Glucose Predictor; PBH, postbariatric hypoglycemia; PBH-DS, PBH detection system.

(up to 2 h of data) and the current ROC. Given the noisy nature of the CGM ROC, a smoothed version (ROC_F) is calculated using a four-sample moving-average filter. The algorithm switches between three modes of operation as illustrated in Figure 3.

The operation modes are:

- ''Waiting for meal'' is the default state. If the three most recent estimated ROC_F were >1 mg/dL/min, the system assumes that a meal has been consumed and switches the state to ''waiting for peak.''
- In the ''waiting for peak'' state, the system waits for the ROC sign to change. When $ROC_F < 0$, the postprandial glycemic peak is detected, and the algorithm registers the time (t_{PEAK}). The average ROC_F (G'_{MEAL+}) of the CGM signal in the previous 45 min is also registered, as an estimation of the rate of glucose ascent for the detected meal. An estimation of the potential time to hypoglycemia is then calculated:

$$HTime_{MEAL} = t_{PEAK} + \frac{G_F(t_{PEAK}) - th}{G'_{MEAL+}}, \quad (1)$$

where G_F is the filtered value of the CGM after applying the noise-spike and low-pass filters described in the original LGP article[35] (with the modified parameters described below), and $HTime_{MEAL}$ is the estimated time of hypoglycemia for the current meal. $HTime_{MEAL}$ is not intended to be an accurate representation of the actual PBH alarm time but rather a limit of operation of the PBH alarm, that is, PBH alarms are expected to happen before $HTime_{MEAL}$, as described in Equation (2). th = 75 mg/dL is the hypoglycemic threshold.

- ''Waiting for hypoglycemia'' mode is activated when a meal peak is detected. In this state the system observes the CGM trend until a hypoglycemia event is detected or 2 h have passed from t_{PEAK}.

The prediction of hypoglycemia (once a meal has been detected) is based on the original LGP[35] with the following parameter values: $\Delta G = 5$ mg/dL/min, $\tau_F = 3$ min, $\#al = 1$, $ph = 30$ min, $G_{MAX} = 150$ mg/dL, $G'_{MAX} = -0.5$ mg/dL/min, and $G'_{MIN} = -5$ mg/dL/min. The choice of these values for the parameters allows PBH alarms to be triggered faster than the original LGP algorithm. In addition, a new condition is added as a requirement for a PBH alert:

$$tlow + t(k) \leq HTime_{MEAL} + hypo_w, \quad (2)$$

where $hypo_w = 10$ min is a new user-defined parameter and $t(k)$ is the time at current sample k. This condition is necessary but not sufficient for a PBH alarm, since *tlow* (estimated time for glucose to be lower than *th*) also needs to be lower than *ph*. This new condition guarantees that the PBH alarm will be triggered when glucose is rapidly decreasing after a meal. For slowly dropping postprandial glucose profiles, the detection relies on the LGP* alarm.

LGP alarm.* This module was based on the *PBH-DSv001*, with its parameter values altered to better cope with the patterns observed in PBH participants from stage A: $\Delta G = 5$ mg/dL/min, $\#al = 2$, $ph = 20$ min, and $G'_{MIN} = -5$ mg/dL/min. ΔG was increased to relax the noise-spike filter against the fast-changing glucose profiles observed. $\#al$ was increased to 2 (two consecutive instances of detection by the LGP* algorithm) to avoid false alarms caused by the noisy nature of CGM sensors.

Study endpoints. This iterative development clinical study was designed to evaluate the primary endpoints of safety and feasibility of the proposed system to predict and prevent severe hypoglycemia in patients with PBH. Secondary outcomes included prediction of imminent hypoglycemia by the automatic monitoring algorithm, minimization of time below a prespecified threshold (<75 mg/dL) using glucagon delivery, prevention of

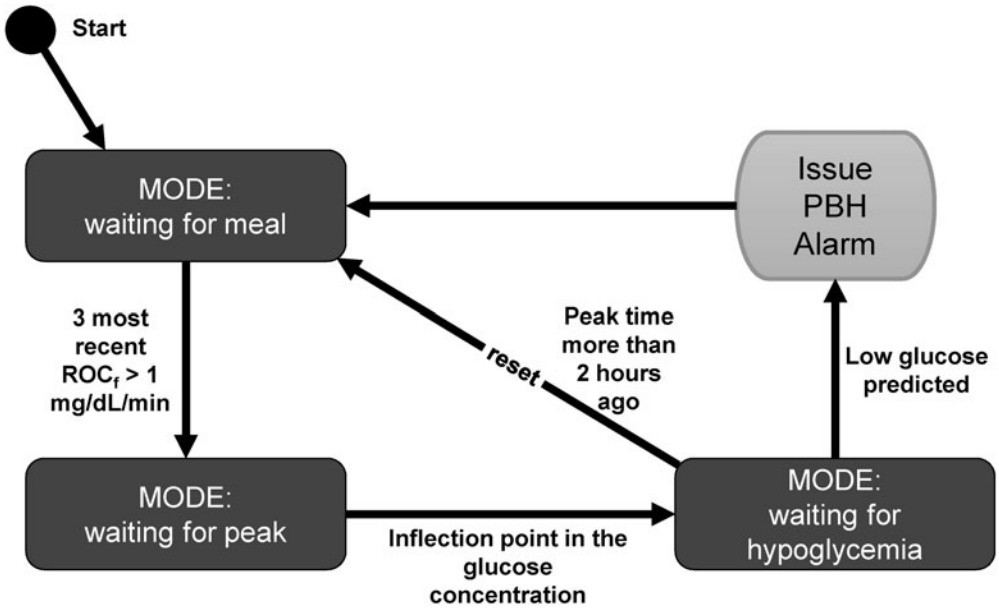

FIG. 3. Flowchart of the PBH-DS states. The algorithm sequentially switches between three modes of operation depending on the glucose history at each time stamp.

Table 1. Participant Characteristics

	Mean (median)	*Count (range)*
Gender (M:F)		1:6
Age (years)	51	(38–62)
Months postop hypoglycemia diagnosed	(41)	(12–150)
Months postop at study visit	116	(45–176)
Hemoglobin A1c (%)	(5.7)	(5.4–5.8)
Preoperative BMI (kg/m^2)	46.4	(37.8–61.0)
Current BMI (kg/m^2)	30.1	(24.3–36.8)
Delta BMI (kg/m^2)	−16.3	(−36.7–−5.2)
Prescribed glucose-modifying medications		6 of 7
Received nutritional counseling		7 of 7
Comorbid conditions		
Depression		6 of 7
Nephrolithiasis		3 of 7
History of hypertension		4 of 7
History of obstructive sleep apnea		5 of 7
History of diabetes		1 of 7

Normally distributed data are expressed as mean; skewed data are expressed as median.
BMI, body mass index.

severe postprandial hypoglycemia (plasma glucose <60 mg/dL), and prevention of rebound hyperglycemia (plasma glucose >180 mg/dL) after glucagon delivery.

Results and Discussion

Participant characteristics

Six females and one male were enrolled, with mean age 51 years (range 38 – 62), mean current body mass index (BMI) 30.1 (range 24.3 – 36.8) kg/m^2 with a mean BMI delta of −16.3 (range −36.7 to −5.2) kg/m^2, median hemoglobin A1c 5.7% (range 5.4% −5.8%), and mean postoperative duration 116 months (range 45 – 176 months). Two participants enrolled twice, in different stages of system development (Table 1 and Supplementary Table S1; Supplementary Data are available at http://online.liebertpub.com/doi/suppl/10.1089/dia.2017.0298).

All participants reported severe hypoglycemia with neuroglycopenia first occurring between 12 and 150 months after surgery. All had received education about medical nutrition therapy[39] and six were on antihypoglycemic medications (e.g., acarbose, short-acting octreotide, and diazoxide some in combination) at enrollment. One participant had a history of gestational diabetes mellitus but there was no other history of diabetes mellitus.

Mixed meal tolerance testing

Graphical depiction of a representative participant from each stage of development of the glucagon pump system is shown in Figure 4, including glucose (both sensor and plasma), insulin, glucagon, and C-peptide concentration data. Algorithm-generated alarms and glucagon delivery are indicated at the top of each plot. Numerical values for relevant metrics are provided in Table 2.

Mean fasting plasma glucose was similar for all participants (85 ± 5 mg/dL), with corresponding insulin 3 ± 3 μU/mL and median C-peptide 1.25 (0.2, 1.5) ng/mL; these values are within the normal fasting range, as is typical for PBH. No hypoglycemia was reported by participants during the night before the mixed meal tolerance test. One participant had a detectable baseline glucagon (127 pg/mL); all others were below the lower limit of quantification for the assay (<100 pg/mL). After the meal challenge, all participants had a rapid rise in sensor glucose, reaching a mean peak plasma glucose of 208 ± 19 mg/dL. Subsequently, sensor glucose rapidly declined, at a mean ROC of −6.6 ± 3.7 mg/dL/min.

Implementation of the PBH-specific detection algorithm. The *PBH-DSv.001* prediction algorithm successfully generated alerts before reaching the sensor threshold for the first two participants (stage A), with sensor glucose values of 89 and 81 mg/dL, respectively. However, plasma glucose values were already below the plasma threshold of 75 mg/dL at the time of the alarm (68 and 71 mg/dL), in violation of our primary endpoint. Despite glucagon administration, subsequent nadir sensor glucose values were 58 and 62 mg/dL with corresponding plasma glucose 57 and 49 mg/dL, respectively.

Sensor-based estimation of glycemia is known to lag behind plasma concentrations of glucose[40]; this pattern is exacerbated when glucose levels are rapidly changing, as in the postprandial state in PBH. Indeed, sensor glucose was 21 and 10 mg/dL greater than plasma levels at the time of the alarm for the first two participants.

Given the rapid declines in glucose in the postprandial state observed in the first two participants (up to −11 mg/dL/min) and the sensor lag, the PBH-DS was updated to allow for earlier prediction of hypoglycemia in the next stages of development. Meal-related glucose excursions and peaks were identified, which then triggered implementation of the PBH-specific algorithm at a higher glucose threshold (i.e., when sensor glucose was <150 mg/dL), using an extended prediction window (30 min), and limiting ROC to 5 mg/dL. The new algorithm (*PBH-DSv002*) was capable of issuing alerts earlier, and a posteriori simulations demonstrated that alarms would have been triggered 25 and 45 min earlier than with the stage A algorithm (*PBH-DSv001*), allowing earlier glucagon delivery.

Using the new *PBH-DSv002*, glucose concentrations were higher at the time of the hypoglycemia alert for participants studied under stages B, C, and D, ranging from 80 to 140 mg/dL for sensor glucose and from 75 to 91 mg/dL for plasma glucose (Fig. 5A). Nadir plasma glucose was higher for stages B, C, and D (62, 59, and 75 mg/dL, respectively, versus 53 mg/dL for stage A), and nadir sensor glucose also increased progressively from stages A to D (60, 61, 65, and 72 mg/dL, respectively, Fig. 5A). Similarly, the sensor time below threshold (after the initial hypoglycemia alarm) was reduced progressively from stages A to D (77%, 55%, 27%, and 11%, respectively, Fig. 5B).

Oral glucose treatment. Glucose tablets were administered to two participants in stage B and to two in stage C (Supplementary Table S2). No rebound hyperglycemia was observed in any participant.

Connectivity. During the study visit for the final stage of the system development, and 50 min after the first glucagon dose, there was a 25 min disconnection in the CGM-pAPS channel until the system was reset. The second glucagon dose for stage D was given 7 min after the signal loss notification

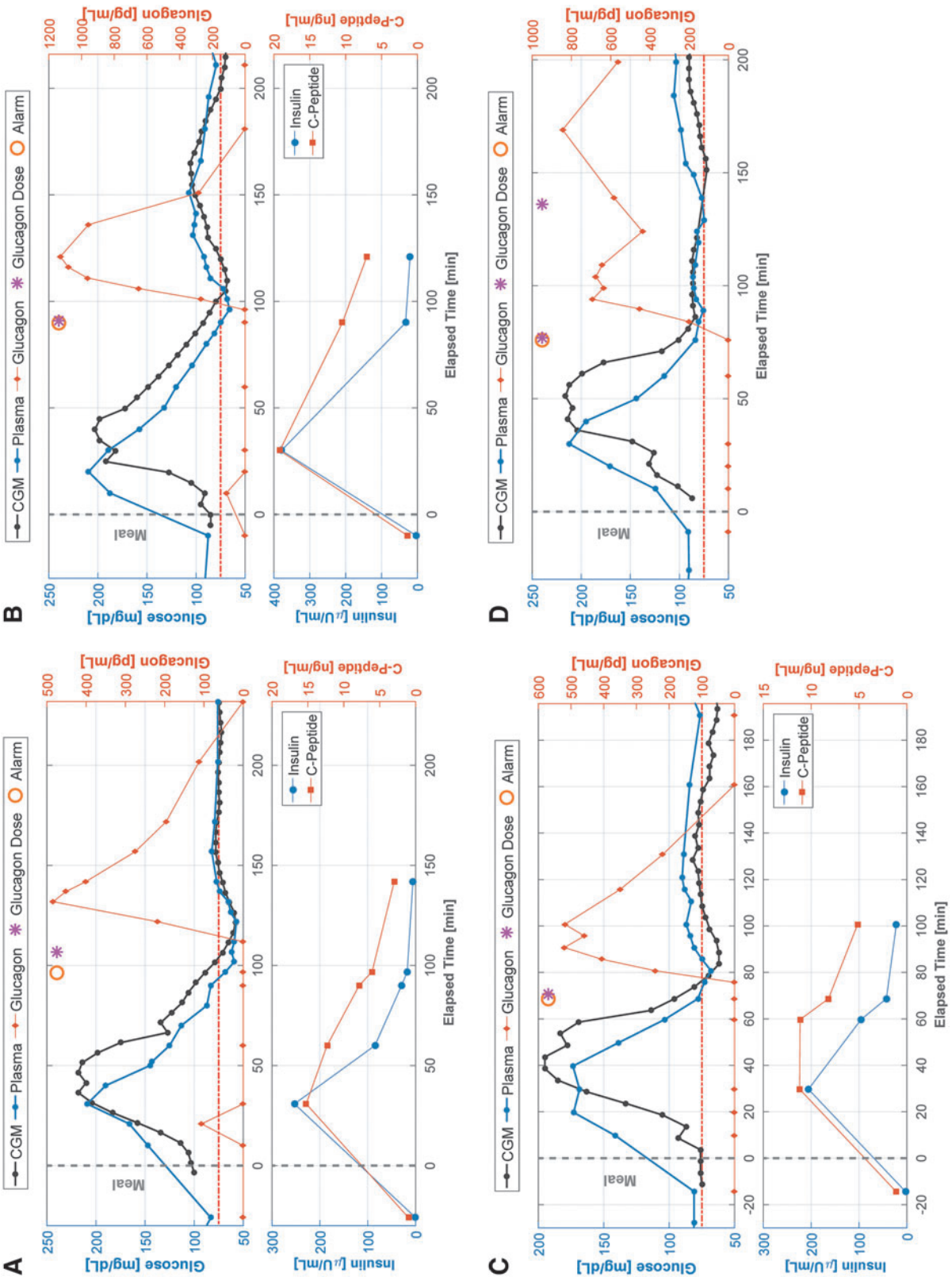

FIG. 4. **(A–D)** Data from a representative participant from each stage of system development (stages A–D corresponding to **A–D)**. For each, the top plot shows sensor (black) and plasma (blue) glucose and glucagon concentrations (orange). The bottom plot displays insulin (blue) and C-peptide (orange) concentrations (**A–C**). Insulin and C-peptide concentrations were unavailable from the participant in stage D due to technical assay issues. The time stamps for the algorithm alarm and glucagon delivery are indicated by marks on the top of each plot.

Table 2. Prediction Alarms, Glucose, Glucagon, Insulin, and Time Intervals During the Mixed Meal Tolerance Test

			Group A		Group B			Group C			Group D
			A-1	A-2	B-1	B-2	B-3	C-1	C-2	C-3	D-1
Baseline	Glucose (mg/dL)	Sensor	95	73	75	72	83	81	69	89	82
		Plasma	83	82	81	83	94	88	77	88	91
	Insulin (μU/mL)		0	0	3	7	5	5	0	3	n/a
	C-peptide (ng/mL)		0.987	1.44	1.14	5.15	0	1.58	0	1.36	n/a
Postmixed meal	Peak glucose (mg/dL)	Sensor	218	197	195	240	180	231	219	203	216
		Plasma	209	195	174	232	216	193	232	210	213
	Peak insulin (μU/mL)		253	221	206	243	247	871	85	379	n/a
	Peak C-peptide (ng/mL)		15.23	15.85	11.2	21.28	23.68	35.32	19.21	19.17	n/a
	Minimum glucose ROC (mg/dL/min)	Sensor	−10	−9	−11	−2	−3	−3	−4	−5	−12
Hypoglycemia alarm	Glucose (mg/dL)	Sensor	89	81	96	80	116	140	86	93	101
		Plasma	68	71	78	81	91	79	80	75	84
	Insulin (μU/mL)		18	11	43	3	244	184	11	33	n/a
	C-peptide (ng/mL)		6.06	5.87	8.19	6.72	19.75	19.21	7.46	10.45	n/a
	Mixed meal to alarm (min)		96	118	69	164	73	100	140	90	76
	Alarm to glucagon delivery (min)		10	12	2	4	5	1	0	1	1
Postglucagon	Nadir glucose (mg/dL)	Sensor	58	62	62	53	67	73	55	68	72
		Plasma	57	49	68	60	59	53	59	66	75
	Peak glucagon (pg/mL)		484	319	520	319	175	664	490	1130	845
	Insulin (μU/mL) at 30 min		6	7	22	9	63	n/a	12	21	n/a
	C-peptide (ng/mL) at 30 min		3	n/a	5.2	5	8.7	n/a	5.3	7.06	n/a
	% Time glucose ≤75 mg/dL	Sensor	73	100	58	88	32	8	59	29	11
		Plasma	67	92	23	46	39	88	36	29	7
	Oral CHO required (g)		0	0	0	16	23	40	8	0	0

Metrics are reported per study stage. The participants are arranged in the order that the study was performed. Note that for metrics occurring at alarm or thereafter (including the time of the alarm), timing is stage dependent due to modifications in hypoglycemia detection methods and study drug dosage.

CHO, carbohydrate; n/a, not available; ROC, rate of change.

by pAPS, when the sensor glucose fell below the 75 mg/dL threshold, although no alarm was received.

Hypoglycemia symptom scores. At the time of hypoglycemia prediction alert, participants reported autonomic, neuroglycopenic, and nonspecific symptoms, with scores greater than baseline (Fig. 6). Symptom scores remained 18% above baseline by 15 min, decreased to or below baseline by 30 and 60 min after glucagon bolus. By contrast, the ''dummy symptoms'' score did not change significantly from baseline

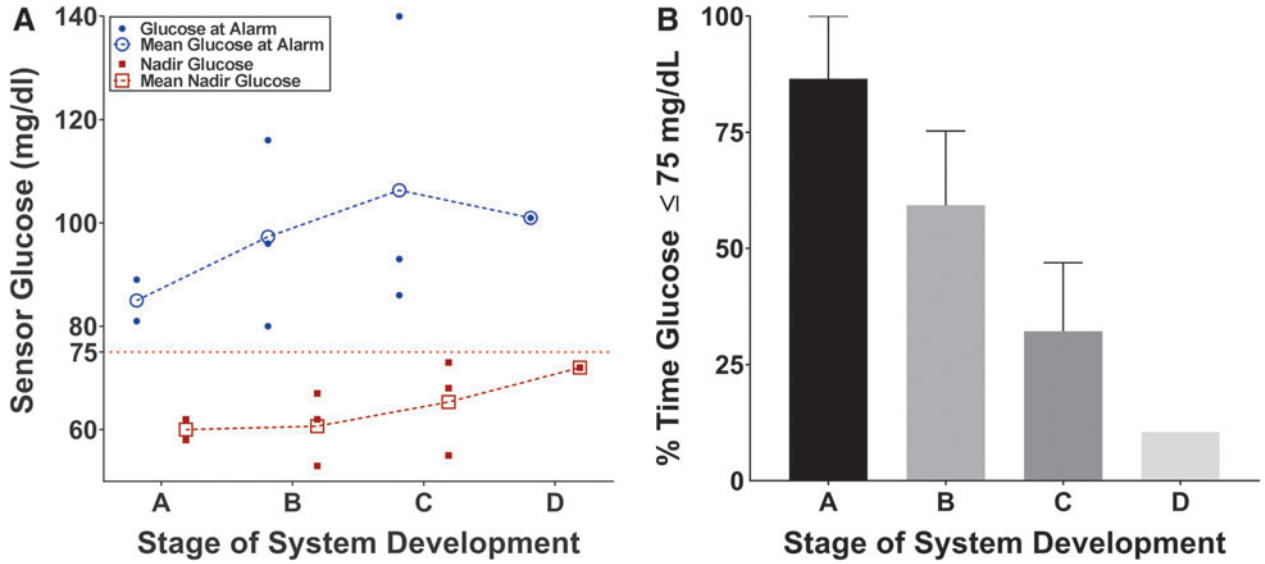

FIG. 5. **(A)** Sensor glucose at time of hypoglycemia prediction alarm (blue symbols) and at nadir (red symbols). Blue symbols indicate individual (solid circle) and mean (outlined circle) sensor glucose at time of the hypoglycemia prediction alarm. Red symbols indicate individual (solid square) and mean (outlined square) nadir sensor glucose values during the 2 h observation period after the hypoglycemia alert. **(B)** Percentage time when the sensor glucose was ≤75 mg/dL during the 2 h observation period after glucagon delivery. Bar height represents mean percentage time and error bars represent the standard error of the mean.

at any time point measured. Symptom scores were substantially lower at all time points during the last stage of development.

Adverse events. In five study visits, participants described varying degrees of discomfort at the glucagon infusion site, typically lasting for the duration of infusion. The infusion site was examined by the study physician at 30 and 60 min after glucagon administration and again by the participant 24 h later. At 30 min, well-defined erythema was identified in four, moderate erythema in two, and barely perceptible erythema in three study visits. By 60 min, well-defined erythema was present in five study visits, whereas moderate erythema resolved, and four study visits had barely perceptible residual erythema. At 24 h after the meal test, all participants reported complete resolution of any skin changes at the infusion site. Nausea or headache was documented during five and three study visits, respectively. No participant had systemic rash and there were no serious adverse events.

Hormonal evaluation. There was a robust rise in insulin after meal ingestion as previously,[9,10] with peak median insulin of 245 (210, 348) μU/mL and peak mean C-peptide of 20 ± 7 ng/mL at 30 min. At the time of the hypoglycemia alert, median insulin and C-peptide levels had decreased to 25.5 (11, 149) μU/mL and 8 (6, 17) ng/mL, respectively. Thirty minutes after glucagon infusion, insulin and C-peptide levels remained stable, with median insulin 12 (7, 22) μU/mL and mean C-peptide 6 ± 2 ng/mL.

In contrast to prior studies demonstrating increased postmeal glucagon concentrations in postbypass patients, both with and without neuroglycopenia,[9,10] postmeal glucagon levels remained below assay detection limit in all but two of nine study visits in this study. Glucagon levels were undetectable at the time of predicted hypoglycemia alert. After glucagon infusion, peak glucagon levels were 387 ± 141 pg/mL for the 150 μg dose (stages A/B), values similar to those achieved in prior mini-dose glucagon studies.[29,41,42] Average glucagon values were twofold higher (782 ± 273 pg/mL) for the high dose and multi-dose study visits (stages C/D).

Post-study, HPLC analysis of the glucagon stock determined that the fixed injection volume of 30 μL used in the study provided $\sim 110 \pm 5$ μg of investigational glucagon for the first five participants in stages A and B. In stages C and D, a new stock of investigational glucagon was used; HPLC analysis determined that each 60 μL injection provided 240 μg of glucagon.

A posteriori simulations. CGM data from all study visits were used to simulate the performance of both versions of the detection algorithm (*PBH-DSv001* and *PBH-DSv002*) to evaluate the advantages of the latter over the original. An example of these simulations is shown in Figure 7, with numerical results of simulations summarized in Table 3.

On average, the final version of the algorithm (*PBH-DSv002*) triggered alarms significantly earlier (mean $t_1 = 15$ min, $p = 0.031$). Mean glucose at the time of the alarm was also significantly higher for the final version of the algorithm (mean difference 24 mg/dL, $p = 0.031$). In six out of nine simulations using *PBH-DSv002*, the postprandial nadir glucose was preceded ($t_2 > 0$) by a second alarm, which occurred on average 56 min after the first alarm. *PBH-DSv001* produced

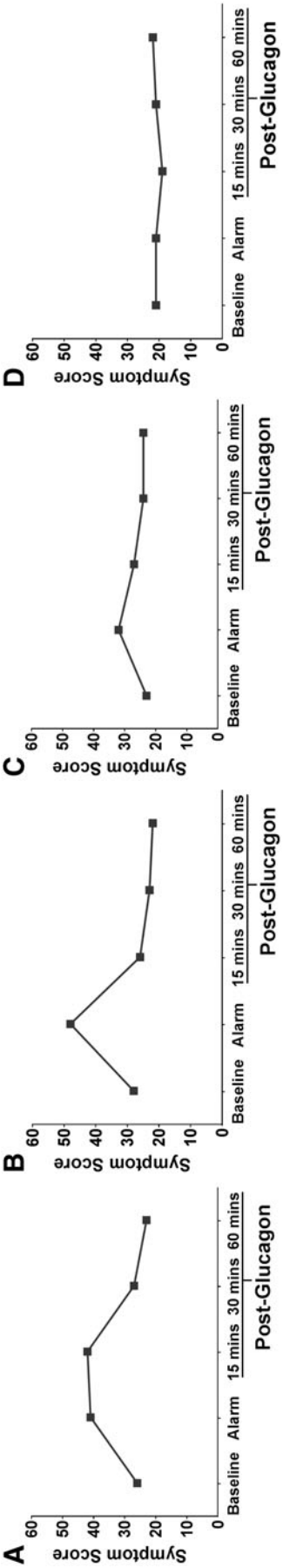

FIG. 6. Modified Edinburgh Symptom Score. Autonomic, neuroglycopenic, and nonspecific symptoms were collected at baseline, at the time of the hypoglycemia prediction alarm, and at 15, 30, and 60 min after glucagon bolus. Panels **A**, **B**, **C**, and **D** correspond to a representative participant visit in each stage of the system development. Panels **A** and **D** are from the same participant who enrolled in the first and final stages of system development.

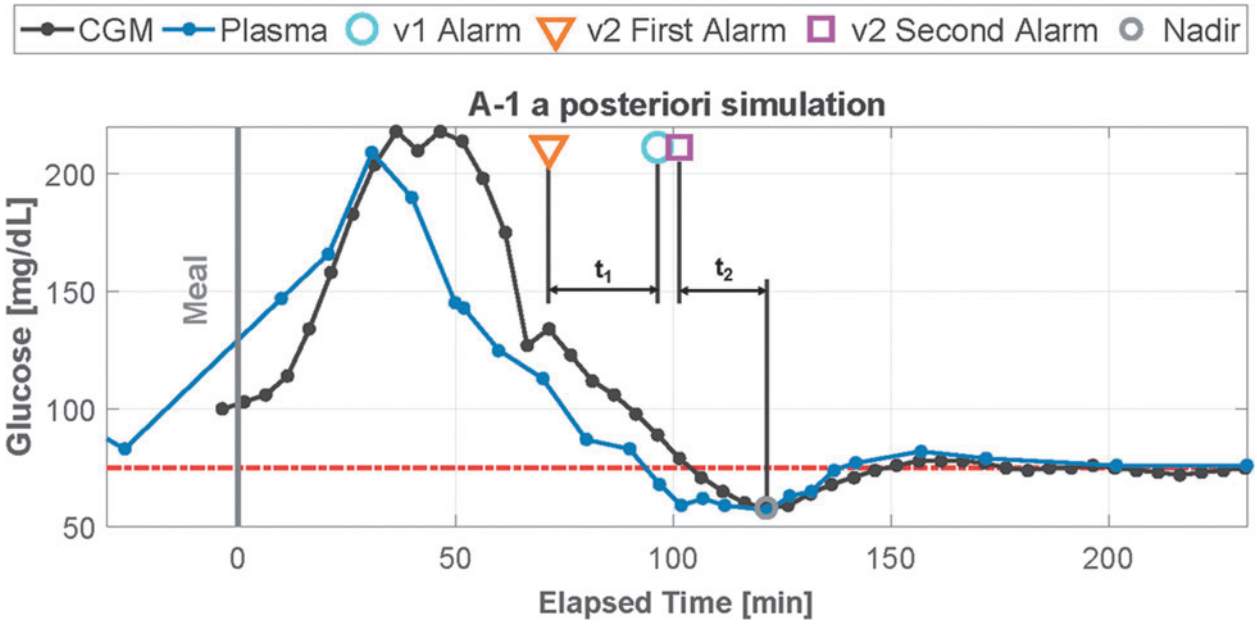

FIG. 7. A posteriori simulation of data from study visit A-1. The simulated alarm by the *PBH-DSv001* algorithm is indicated by the cyan circle. The alarms simulated by *PBH-DSv002* are displayed in orange (triangle) and in purple (square). The cyan circle alarm coincides with the alarm that was used in the study visit. Nadir sensor glucose is highlighted in gray. $\mathbf{t}_1$ indicates the time difference between the first (and only) alarm of *PBH-DSv001* and the first alarm given by *PBH-DSv002*. Positive values of $\mathbf{t}_1$ correspond to *PBH-DSv002* alarms occurring *before PBH-DSv001* alarms. The value of $\mathbf{t}_1$ for the displayed simulation is 25 (min). $\mathbf{t}_2$ indicates the time difference between the time of the nadir sensor glucose value and the second alarm given by *PBH-DSv002*. Positive values of $\mathbf{t}_2$ correspond to the second alarm occurring *before* the nadir glucose. The value of $\mathbf{t}_2$ for the displayed simulation is 20 (min).

false positive alarms shortly after meal ingestion in five patients, whereas the final algorithm produced none.

Discussion. A novel detection algorithm, designed for the unique postprandial glycemic patterns characteristic of PBH, was developed and refined over the course of the study. During the first two participant visits (stage A), both the alarm and subsequent manual glucagon delivery were too late to achieve our primary endpoint, namely prevention of plasma glucose <75 mg/dL. A modification of the prediction algorithm led to earlier alarms, maintained specificity, and translated into improved prediction power in the final seven participants, all of whom had glucose levels above threshold at the time of the alarm. Comparative computer simulations show that the final prediction algorithm is capable of triggering alarms significantly earlier and at glucose values significantly higher than those triggered by the initial algorithm implemented. This greater prediction power creates a greater time buffer during which the glucagon dose can reach its onset of action, effectively reducing risk of hypoglycemia. The simulations also showed that the addition of a second alarm and a second glucagon dose (stage D) could have increased the nadir glucose and avoided hypoglycemia occurring later in the postprandial period. This is clearly observed in the simulation shown in Figure 7, in which a timely second dose given at the time of the second alarm could have prevented the hypoglycemic event occurring 20 min later.

TABLE 3. A POSTERIORI SIMULATIONS OF THE NINE GLUCOSE PROFILES FROM THE STUDY USING BOTH VERSIONS OF THE DETECTION ALGORITHM

		Stage A		*Stage B*			*Stage C*			*Stage D*
		A-1	*A-2*	*B-1*	*B-2*	*B-3*	*C-1*	*C-2*	*C-3*	*D-1*
Detection system used in stage A	Sensor glucose at time of alarm (mg/dL)	***89***	***81***	62	84	79	85	86	93	87
Detection system used in stages B, C, and D (first alarm)	Sensor glucose at time of alarm (mg/dL)	134	115	***96***	***80***	***116***	***140***	***86***	***93***	***101***
	Time difference between v1 and v2 alarms ($\mathbf{t}_1$) (min)	25	45	***15***	***–5***	***15***	***20***	***0***	***0***	***20***
Detection system used in stage D (second alarm)	Sensor glucose at time of alarm (mg/dL)	79	81	74	70	67	77	76	80	***79***
	Sensor nadir glucose (mg/dL)	58	62	62	53	67	73	55	68	***72***
	Time difference between nadir and second alarm ($\mathbf{t}_2$) (min)	20	25	–75	50	0	55	50	–85	***15***

Bold italic values indicate that the simulations coincide to the experimental setup tested in the clinical setting for that visit.

Boluses delivered through the glucagon pump acutely raised serum glucagon and at the doses employed were not associated with increased insulin or C-peptide concentrations. Nadir glucose and time spent under 75 mg/dL after the glucagon bolus were reduced progressively with each stage of protocol development, which involved either earlier hypoglycemia alarms or larger glucagon doses. Rescue oral glucose was not given to the first two participants in stage A due to lack of symptoms of hypoglycemia. However, rescue glucose was given in subsequent stages for symptomatic hypoglycemia or asymptomatic glucose levels <60 mg/dL; although this may have impacted the time under 75 mg/dL, it would not have impacted the glucose level at the time of glucagon administration.

Severe hypoglycemia in PBH often occurs after a high-carbohydrate mixed meal. Although a central goal of medical nutrition therapy is to reduce consumption of simple carbohydrates,[39] we used a high-carbohydrate provocative test meal to mimic conditions contributing to severe hypoglycemia. We designed the hypoglycemia detection algorithm to work successfully under a worst-case scenario, such as after consumption of a high-glycemic index, rapidly absorbed meal. Indeed, use of the algorithm under less provocative conditions might permit even more robust functionality of the hypoglycemia prevention system.

Nevertheless, in our test conditions, low nadir glucose and/or incomplete reversal of postprandial declines in glucose, despite glucagon infusion, may have resulted from several factors. First, postmeal insulin concentrations were high, contributing to subsequent rapid declines in glucose. Such high insulin levels cannot be fully cleared within the timeframe of the postprandial absorption period, leading to an imbalance between glycemia and residual high insulin concentrations. Moreover, insulin signal transduction and glucose uptake in insulin-responsive tissues continue long after plasma insulin levels have decreased, contributing to sustained hypoglycemic effects. Second, the endogenous counter-regulatory response to hypoglycemia is likely impaired in PBH, as reported for other post-RYGB patients.[13,14] Glucagon levels were undetectable in all participants at the time of the hypoglycemia alarm. Third, the required human response to the automatically generated alarm resulted in a time delay in glucagon delivery. Although the delay was reduced after optimization of the protocol in stages B, C, and D, fully automated closed-loop systems may be even more effective to overcome this delay. Finally, the doses of glucagon utilized in this study (150–600 μg, delivered in two doses) are all substantially smaller than standard rescue doses in emergency kits (1 mg), and may not be sufficient in the setting of high ambient plasma insulin and/or sustained tissue insulin action in PBH.

Since this was the first implementation of the Xeris glucagon formulation in minidoses in PBH, the dosage was chosen with caution to prevent the rebound hyperglycemia previously observed with higher rescue doses of glucagon.[23] Based on the current results, the glucagon dosage required to effectively prevent postprandial hypoglycemic events will likely need to be patient dependent, delivered in multiple instances, and in doses ≥300 μg. Repeated minidoses, such as those implemented in the participant in stage D, may be required to completely prevent hypoglycemia; this will be evaluated in follow-up studies.

This study also demonstrates the considerable interindividual variability in insulin secretion in response to a standardized mixed meal and response to glucagon treatment. For instance, participant C-1 had significantly higher postprandial insulin level and also required significantly more oral glucose to mitigate hypoglycemia. This participant had a history of gestational diabetes; we can speculate that dysregulation of glucose-dependent insulin secretion may have been present before surgery. After insulin sensitivity was improved with RYGB-mediated weight loss, it is possible that insulin secretion was not appropriate for the new level of insulin sensitivity. In addition, substantial variability in islet mass has been observed in patients with PBH,[43] potentially contributing to interindividual differences. Finally, the doses of glucagon, which were based on delivery of a fixed volume from stocks of glucagon for which concentration had been previously determined by HPLC analysis, were actually 20%–25% lower than the targeted value due to both analytical technique and expected losses due to drug degradation.

We acknowledge several limitations of this pilot study. Sample size was small; gender mix, although unequal, is typical of the PBH population at our institution. The protocol was modified at every stage to test successive iterations of the detection algorithm and/or increasing glucagon doses to prevent hypoglycemia; future approaches will mimic the stage D implementation, employing automatic sequential dosing, which would likely prevent delayed or recurrent hypoglycemia. Furthermore, a larger or individualized dose of glucagon based on other factors could improve responses.

The bioavailable dose of glucagon delivered in our study was less than we had originally calculated, but still within manufacturer-specified tolerances. Participants in stage A did not receive oral glucose treatment per protocol due to lack of symptoms, which may have led to lower nadir glucose values in those two participants. There was one event of lost connectivity in the final stage, resulting in the only missed hypoglycemia alert (false negative error) among the four study stages. A posteriori analysis of the CGM data for that event showed that an alarm would have been triggered 10 min before the actual time that glucagon was delivered, potentially avoiding the hypoglycemic event completely.

In conclusion, we report the first use of an event-based glucagon delivery system, which (1) utilized data from CGM to predict impending hypoglycemia and (2) prevented severe hypoglycemic episodes in participants with severe PBH under conditions of a high-carbohydrate liquid mixed meal. The single-dose glucagon utilized in the first three stages of our study was well tolerated but ultimately ineffective in avoiding mild hypoglycemia. With development and implementation of a novel algorithm development designed for the unique PBH population, nadir glucose levels and time spent below hypoglycemic threshold improved at each stage.

Although our proof-of-concept study was not powered to assess significant differences in secondary endpoints, the preliminary results are encouraging. Individualized doses of glucagon may be required to fully reverse rapid postprandial falls in glucose in the setting of very high peak postprandial insulin levels in PBH. Our iterative development clinical study supports feasibility and need for follow-up trials in both the clinical research unit and outpatient settings to determine whether a multidose protocol similar to stage D, deployed in a fully automated system, can significantly reduce or even prevent hypoglycemic episodes for patients with PBH.

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Disclosure Statement

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