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Postprandial Glycemic Excursions with the Use of a Closed-Loop Platform in Subjects with Type 1 Diabetes: A Pilot Study

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Abstract

Background:

The aim of this study was to evaluate the efficacy of a proportional derivative algorithm closed-loop system to control postprandial glucose concentrations in subjects with type 1 diabetes.

Methods:

Six subjects treated with continuous subcutaneous insulin infusion received a standardized meal on three days. The first day served as control, the second day as learning experiment for the algorithm, and the third day to compare the closed loop to the control day. Venous blood glucose was measured as reference until 300 min postprandially. The artificial pancreas platform consisted of a subcutaneous continuous glucose monitor (CGM), the GlucoDay® S (Menarini Diagnostics), two D-Tron+ pumps (Disetronic Medical Systems) for subcutaneous insulin, and glucagon administration connected to a personal computer.

Results:

One subject was excluded due to technical failure of the CGM. Two of five subjects were male, mean age was 50.8 years (range 38–60), and mean hemoglobin A1c was 8.7% (range 7.0–12.2). The mean postprandial venous blood glucose concentration of day 1 was 205 mg/dl (range 94–265 mg/dl) compared with 128 mg/dl (range 128–158 mg/dl) on day 3 (p = .14). Percentage of time spent in euglycemia postprandially on day 1 was 31% versus 60% on day 3 (p = .08). Time spent below 3.9 mmol/liter (70 mg/dl) was 19% on day 1 compared with 11% on day 3 (p = 1.0). Time above 10 mmol/liter (180 mg/dl) on day 1 was 60% versus 29% on day 3 (p = .22).

Conclusion:

The artificial pancreas provided comparable postprandial glycemic control to usual care.

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Abbreviations: (AUC) area under the curve, (CSII) continuous subcutaneous insulin infusion, (CGM) continuous glucose monitor, (MPC) model predictive control

Keywords: closed loop, diabetes, postprandial glucose control, proportional derivative algorithm

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Introduction

Continuous subcutaneous insulin infusion (CSII) combined with a continuous glucose monitor (CGM) and a glucose control algorithm result in an artificial pancreas. Artificial pancreas or closed-loop systems are capable to achieve automated good glucose control in intensive care unit or critical care unit settings.[1,2]

Steil *et al.*[3] and Weinzimer *et al.*[4] tested an artificial pancreas based on a proportional integrated derivative algorithm in a clinical research unit. Mean glucose concentrations were not different from usual care; however, postprandial glucose excursions were higher than with usual care. A manually administered premeal priming bolus could partially overcome this problem. Schaller and coworkers[5] evaluated an algorithm based on model predictive control (MPC) in six subjects with type 1 diabetes during eight hours in the fasting condition. The model normalized glucose concentrations if the glucose level was above 108 mg/dl and then maintained normoglycemia. Hovorka and colleagues[6] evaluated glucose control with an algorithm based on a MPC model in subjects with type 1 diabetes compared with usual care with an insulin pump in three different settings: overnight glucose control starting two hours after dinner, following a premeal with self-determined manual insulin bolus, until the next morning; postprandial glucose control 30 minutes after dinner, comparing rapidly absorbed carbohydrates to slowly absorbed carbohydrates, until the next morning; and glucose control starting two hours after 45 minutes of exercise until the next morning. In all these studies, closed-loop glucose control resulted in more time in target range as compared with conventional care. Data showed similar results for a MPC closed-loop artificial pancreas compared with usual care in 14 subjects.[7,8]

The aim of this study was to test the feasibility of a proportional derivative control algorithm to control postprandial glucose excursions after a single meal in subjects with type 1 diabetes.

Methods

Subjects

Six subjects with type 1 diabetes treated with CSII for more than six months and aged 18–70 years were recruited for the study. All subjects gave written informed consent. The ethics committee of the Academic Medical Center at the University of Amsterdam approved the study.

Study Procedures

In the afternoon before the study visit, a microdialysis glucose sensor (GlucoDay® S, Menarini Diagnostics, Firenze, Italy) was inserted. Subjects were admitted to the clinical research unit of the Academic Medical Center the following morning in fasting condition. An intravenous catheter was inserted into an antecubital vein for blood sampling. During the first test day, the subjects administered a self-determined insulin bolus before a standardized meal of 40 g carbohydrates. During the second and third test days, subjects wore two D-Tron+ pumps (Disetronic Medical Systems, St. Paul, MN) for subcutaneous insulin and glucagon administration, respectively. The CGM sensor, insulin pump, and glucagon pump were connected to a personal computer containing the algorithm. The test started after calibration of the CGM. No premeal insulin bolus was administered when the standardized meal was served. The subjects remained in bed during the test.

The sensor glucose values were read out every 10 s. Every 5 min, an average glucose level was calculated. The second day was a so-called learning day of the algorithm to determine an individual insulin sensitivity factor. This factor was initially calculated on the basis of total daily insulin need and adjusted as needed during the day 2 experiment. During all three test days, venous blood glucose was measured at baseline and every 30 min until 5 h postprandially.

Calibration Procedure

The calibration procedure was performed before starting automated control and repeated in case of a difference between sensor glucose concentration measured by the Glucoday and self-monitored glucose level above 27 mg/dl. The calibration procedure consisted of taking three sensor measurements and the concomitant self-monitored glucose values taken within 10 min. The average difference of the three measurements between the sensor glucose level and the self-monitored glucose was calculated. This average was the correction factor for the sensor glucose value.

Algorithm

The control algorithm employed in this study was designed by Inreda BV (Goor, the Netherlands) and is patented (NL C 1032756; WO 2007/049961 A3). The algorithm can be characterized as a self-learning individualized proportional derivative controller. Insulin delivery is

determined by the difference between current and target glucose and the rate of change of glucose levels. Furthermore, insulin delivery is adjusted for individual insulin sensitivity.

Target blood glucose values can be programmed for a lower and an upper limit. The upper limit was set at 126 mg/dl and the lower limit at 90 mg/dl. Every 5 min, the glucose levels are compared to the target range. There are three operating ranges. First, if glucose values are below the lower limit, a sound signal is generated. The patient can correct the low glucose value by taking carbohydrates. In case of a glucose fall below 58 mg/dl, glucagon is infused according to a formula taking into account the rate of glucose fall. If glucose levels are between the lower and upper limit, the algorithm administers no insulin. If glucose levels are above the upper limit, insulin is infused according to a formula taking into account the rate of glucose rise. Every 7 min, insulin is administered if the glucose levels are above the limit and not falling. If glucose concentration is above 360 mg/dl, the maximum insulin administration rate is reached, i.e., 10 U per 7 min.

Statistics

All postprandial venous blood glucose concentrations on the first day and on the third day were averaged per subject and were compared as paired measurements with the Wilcoxon signed-rank test. Median venous blood glucose concentrations are given with minimum and maximum value. Sensor glucose concentrations are calculated every 3 min. The sensor glucose concentration were averaged per subject and are expressed as area under the curve (AUC). Demographic features are given as mean with range of minimum and maximum. Time spent in euglycemia was defined as the percentage of time the glucose concentrations were between 70 and 180 mg/dl.

Results

Due to failure of the microdialysis filament on day 3, one male subject was excluded. Two of five subjects were male, mean age was 50.8 years (range 38–60), and mean hemoglobin A1c was 8.7% (range 7.0–12.2). The mean diabetes duration was 30.3 years (range 14–45), and the mean CSII duration was 6.7 years (range 2–14) (**Table 1**).

Table 1.
Baseline Characteristics, $n = 5$

	Gender	Age (years)	Hemoglobin A1c (%)	Diabetes duration (years)	CSII duration (years)
1	male	54	7.1	32	3
2	female	60	7.9	26	9
3	female	38	12.2	14	6
4	female	54	10.0	35	2
5	male	57	7.0	45	14
Median all subjects		50.8 (38–60)	8.7 (7–12.2)	30.3 (14–45)	6.7 (2–14)

The median venous blood glucose concentration on day 1 was 205 mg/dl (range 94–265 mg/dl) compared to a median venous blood glucose concentration on day 3 of 157 mg/dl (range 128–158 mg/dl; $p = .14$) (see **Figure 1** and **Tables 2** and **3**). The AUC of the sensor glucose concentration of day 1 [2993 (mg/dl) x minutes, range 1900–4581] did not differ from day 3 [2746 (mg/dl) × minutes, range 2426–3330; $p = 0.5$]. The postprandial glucose values at 120 and 180 min, the venous peak, and nadir blood glucose concentration on day 1 and day 3 were not different (**Tables 2** and **3**).

The percentage of time spent in euglycemia, hypoglycemia, and hyperglycemia is given in **Tables 2** and **3**. On day 3, the subjects tended to have a higher percentage of time spent in euglycemia, measured by venous blood glucose measurements compared with day 1 (31% versus 60%, $p = .08$). No significant differences were seen in time spent in hypoglycemia or hyperglycemia between day 1 and day 3.

On day 1, two hypoglycemic episodes of 20 and 60 min occurred in two subjects. The corresponding venous blood glucose concentration of the first hypoglycemic period was 58 mg/dl. The concentrations of venous blood glucose during the 60 min period were 54, 59, and 59 mg/dl. On day 3, three hypoglycemic episodes occurred in two subjects, lasting 6, 9, and 30 min. During the period of 30 min, the corresponding venous blood glucose level was 58 mg/dl. No venous measurements were taken during the other two periods. In addition, venous blood glucose measurements detected five other episodes of glucose levels below 70 mg/dl in three subjects, with values of, respectively, 58, 65 (twice), and 68 mg/dl (twice). All hypoglycemic periods occurred late postprandially, after 150 min or later.

On day 3, the algorithm was enabled to give alarms. The number of sound alarms and number of the glucagon responses are shown in **Tables 4** and **5**. In total, the sound alarm went off 14 times, range 1–4 per patient. Glucagon boluses were given in two subjects. No nausea was noted.

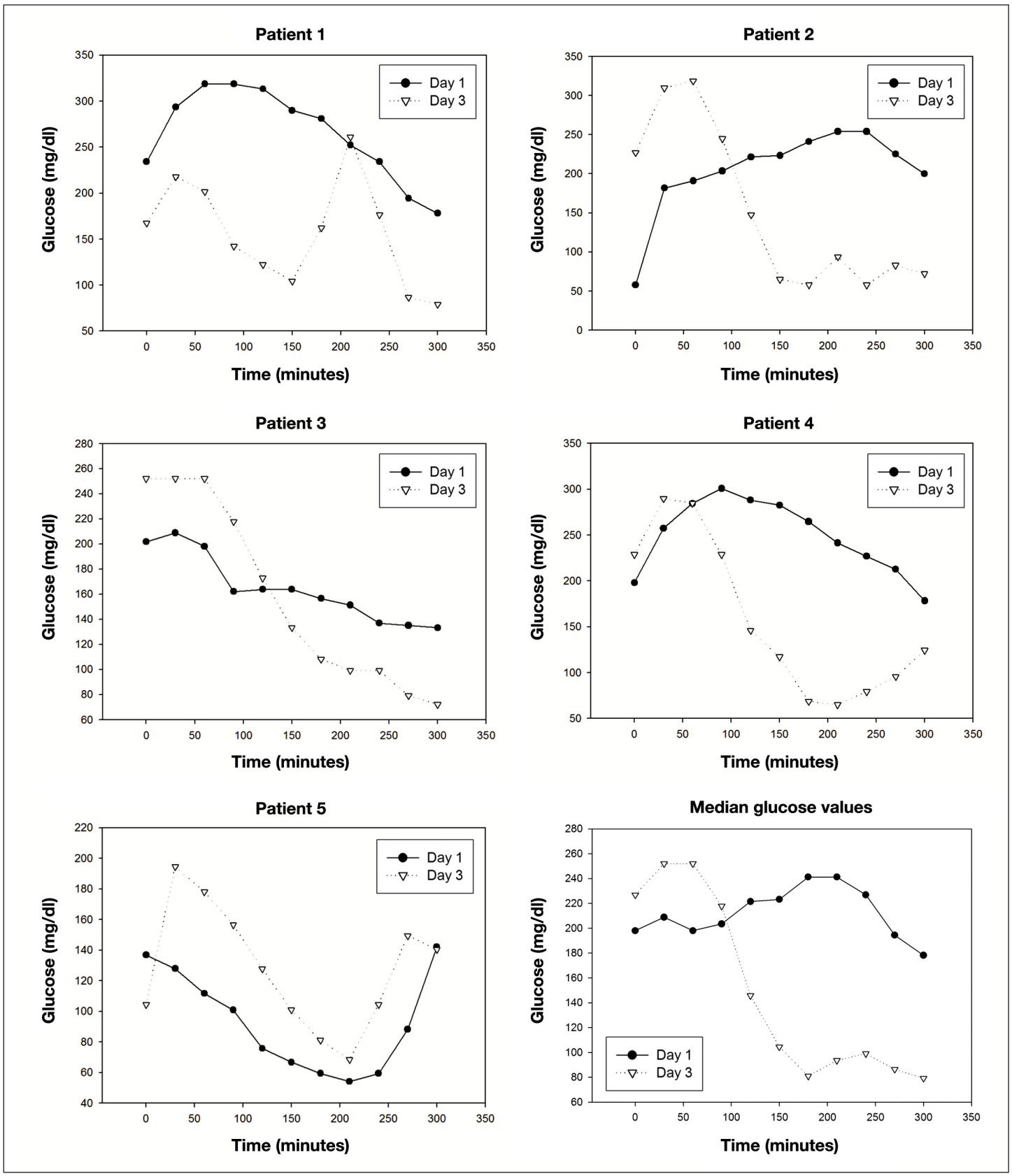

Figure 1. Median Venous Glucose Concentrations on Day 1 Compared with Day 3

Table 2.
Postprandial Venous Blood Glucose Excursions in Milligrams per Deciliter per Subject and Averaged for All Subjects on Day 1 Compared to Day 3, $n = 5$

	Median glucose concentration: day 1	Median glucose concentration: day 3	Percentage of time spent in euglycemia: day 1	Percentage of time spent in euglycemia: day 3	Percentage of time spent in hypoglycemia: day 1	Percentage of time spent in hypoglycemia: day 3	Percentage of time spent in hyperglycemia: day 1	Percentage of time spent in hyperglycemia: day 3
1	281 (178–319)	162 (79–261)	0	61	0	0	100	39
2	221 (58–254)	94 (58–319)	15	39	8	13	78	49
3	162 (133–209)	133 (72–252)	80	54	0	0	21	47
4	257 (178–301)	124 (65–290)	11	49	0	3	90	49
5	88 (54–142)	128 (68–194)	96	68	5	0	0	33
Overall	205 (94–265)	157 (128–158)	31	60	19	11	60	29

Table 3.
Postprandial Venous Blood Glucose Excursions on Day 1 Compared with Day 3, $n = 5$

	Median glucose concentration 120 min: day 1	Median glucose concentration 120 min: day 3	Median glucose concentration 180 min: day 1	Median glucose concentration 180 min: day 3	Median peak concentration: day 1	Median peak concentration: day 3	Median nadir concentration: day 1	Median nadir concentration: day 3
1	313	122	281	162	319	261	178	79
2	221	148	241	58	254	319	182	58
3	164	173	157	108	209	252	133	72
4	288	146	265	68	301	290	169	65
5	76	128	59	81	142	194	54	68
Median all subjects	221 (76–313)	146 (122–173)	241 (59–281)	81 (59–162)	254 (142–319)	261 (194–319)	178 (54–182)	68 (58–79)

Table 4.
Insulin Need During the Study

	Day 1			Day 3
	Bolus	Basal	Total amount of insulin (IU)	Total amount of insulin (IU)
1	14	6.1	20.1	41
2	4	3	7	26.5
3	4	5	9	9
4	4.5	5.8	10.3	40.5
6	5	6.1	11.1	9
All			57.5	126
p value	0.14			

Table 5.
Number of Hypoglycemic Episodes on Day 1 Measured by Venous Blood Glucose Compared with the Number of Sound Alarms on Day 3 If the Glucose Dropped below 5 mmol/liter (90 mg/dl) and the Number of Glucagon Responses If the Glucose Dropped below 3.2 mmol/liter (58 mg/dl)

	Hypoglycemia: day 1	Hypoglycemic alarm: day 3	Glucagon need (IU): day 3
Subject 1	0	3	0
Subject 2	1	4	10
Subject 3	0	1	0
Subject 4	0	4	0
Subject 5	3	2	1

The cumulative mealtime-related insulin requirements on day 1 and day 3 are shown in **Tables 4** and **5**. No significant differences were seen (p = .14).

Discussion

In this small pilot study, the feasibility of an artificial pancreas based on a self-learning individualized proportional derivative algorithm was tested. Postprandial venous blood glucose control was comparable to usual care, with a tendency to a higher percentage of time spent in euglycemia. Also, this pilot study showed the narrow balance between achieving good postprandial glucose control and inducing postprandial hypoglycemia. The increased risk of postprandial hypoglycemia can be explained by two reasons. First, in some subjects, the insulin doses were more than doubled on the test day (day 3) due to lack of prestudy optimization of diabetes regulation and, second, due to aggressiveness of the algorithm.

Glucagon boluses were given to two subjects in order to prevent severe hypoglycemia. The efficacy of low-dose glucagon as a rescue to prevent severe hypoglycemia remains to be shown in subsequent experiments. El Khatib and colleagues also used subcutaneous glucagon injections in a closed-loop glucose control, but glucagon was used to control the glucose concentration within the normal range with frequent injection of small doses, while it was used as rescue compound in our setting.

In the near future, the algorithm will undergo revisions, mainly at the glucose level of the sound alarm. The slope of the glucose drop has to be taken in account if the carbohydrate alarm will go off, and the level will be set lower, probably at 72 or 81 mg/dl. Also, a needle-type sensor will replace the microdialysis sensor because of the technical problem of the microdialysis filament. Furthermore, the study duration and number of subjects will be extended. Hereafter, a wireless connection between the components would enable outpatient testing.

In conclusion, postprandial glucose control using a self-learning individualized proportional derivative algorithm was feasible and gave results comparable to nonoptimized usual care, but there is need for improvement since it induced hypoglycemia too frequently.

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