First Use of Model Predictive Control in Outpatient Wearable Artificial Pancreas

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OBJECTIVE

Inpatient studies suggest that model predictive control (MPC) is one of the most promising algorithms for artificial pancreas (AP). So far, outpatient trials have used hypo/hyperglycemia-mitigation or medical-expert systems. In this study, we report the first wearable AP outpatient study based on MPC and investigate specifically its ability to control postprandial glucose, one of the major challenges in glucose control.

RESEARCH DESIGN AND METHODS

A new modular MPC algorithm has been designed focusing on meal control. Six type 1 diabetes mellitus patients underwent 42-h experiments: sensor-augmented pump therapy in the first 14 h (open-loop) and closed-loop in the remaining 28 h.

RESULTS

MPC showed satisfactory dinner control versus open-loop: time-in-target (70–180 mg/dL) 94.83 vs. 68.2% and time-in-hypo 1.25 vs. 11.9%. Overnight control was also satisfactory: time-in-target 89.4 vs. 85.0% and time-in-hypo: 0.00 vs. 8.19%.

CONCLUSIONS

This outpatient study confirms inpatient evidence of suitability of MPC-based strategies for AP. These encouraging results pave the way to randomized cross-over outpatient studies.

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The reduction of postprandial glucose excursions is a major challenge for artificial pancreas (AP) systems using subcutaneous insulin infusion due to delays associated with this route, as discussed in Cobelli et al. (1). Numerous inpatient studies have shown that model predictive control (MPC) is one of the most promising control strategies to cope with this and other delays of glucose closed-loop control (1 and references cited therein). Until now, MPC has not been used in outpatient settings. Three successful outpatient studies with an AP have recently been reported, using either a heuristic algorithm (hypo/hyperglycemia-mitigation system) (2,3) or a medical-based expert system (4). The first two were 42-h studies in adults with type 1 diabetes using a wearable AP platform based on a smartphone, while the third

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study focused on overnight control in a camp of a large pediatric population using a laptop-based system. In this study, we report for the first time an outpatient study based on an MPC strategy and investigate specifically its ability to control postprandial glucose.

RESEARCH DESIGN AND METHODS

Protocol

This study followed the same protocol as previous outpatient studies presented in Cobelli et al. (2) and Kovatchev et al. (3), to which we refer to for details.

A total of six adults (aged 21–44 years) with type 1 diabetes were studied, two and four patients simultaneously. All participants were experienced insulin pump users, and their usual pump was replaced by an Omnipod Insulin Pump (Insulet Corp., Bedford, MA) for the study. A DexCom Seven Plus sensor (DexCom, Inc., San Diego, CA) was inserted 2 to 3 days prior to trials.

Throughout the study, patients wore the DiAs platform, a portable system developed at the University of Virginia allowing outpatient closed-loop control, already used in Kovatchev et al. (3) and Keith-Hynes et al. (5). The core of the DiAs system is an off-the-shelf smartphone running an Android operating system modified for medical use. The closed-loop controller was implemented on this device. Communications between DiAs and pump/sensor were wireless, allowing the patient to move around freely. Since wireless communication is not available on the pump or the sensor themselves, the system included a connection device that communicates wirelessly with DiAs.

The study started at 18:00 on day 1 and lasted for 42 h. Standard sensor-augmented pump therapy was performed with the DiAs set in open-loop mode (i.e., patient-driven), for the first 14 h of the study (day 1 at dinner and night 1). From day 2 at breakfast to day 3 at 12:00, the closed-loop controller was active and challenged by four meals and one night. Both in open-loop and closed-loop modes, dinners were consumed in a local restaurant. Patients were asked to tell the system the estimated meal carbohydrate content. Both in open- and closed-loop modes, they were assisted in the estimation process by the attending clinician, if needed, to avoid gross estimation errors biasing the comparison. In open-loop mode, meal bolus was computed by the pump bolus calculator formula using patient-specific parameters (carbohydrate/insulin ratio and correction factor). In closed-loop mode, the DiAs-based controller computed premeal bolus according to the same patient-specific parameters but also taking into account predicted future glucose values. To avoid potential learning of optimal bolus doses from the first dinner that would have favored the closed-loop intervention, the same patient-specific carbohydrate/insulin ratio and correction factors were used in both open- and closed-loop dinners. In both cases, premeal bolus was delivered 15 min ahead of the meal.

The subjects spent the night in a hotel near the Padova University Hospital, and during the study, the subjects were free to move around the facility and its vicinity.

The subjects interacted with DiAs using a Graphical User Interface, which allows sensor calibrations, meal announcement, etc.

To enhance patient safety, patient data were streamed by DiAs in real time to a telemonitoring website (6). Accessing to the website via an ordinary PC, the study team was able to monitor from remote location the status of the patient and check the correct functioning of the system throughout the trial without interfering/interacting with the experiment unless requested by protocol safety measures or for system troubleshooting.

The study was approved by the local ethics committee and registered with ClinicalTrials.gov as NCT1447992. Written consent was obtained.

Methods

The implemented control algorithm is a modular MPC, presented in Soru et al. (7) and Patek et al. (8). It is an evolution of a previous algorithm exposed in Magni et al. (9), used in an inpatient study, as described in Breton et al. (10). A key improvement concerns meal control. The standard basal/bolus therapy is used as reference in the optimization problem, so that MPC can adapt meal bolus using information about the patient status.

Data Analysis

Data portions affected by system malfunctioning have been removed (overall, the system worked successfully 90.27% of the time). We focus on meals, particularly on dinner.

RESULTS

Overall, the system worked successfully 94.5% during open-loop and 88.3% during closed-loop. No hypoglycemia requesting a third-party assistance and no episode with β-ketones $>$1.0 mmol/L or HemoCue $>$400 or $>$300 mg/dL for $>$1 h were recorded, and no experiment had to be discontinued due to adverse events.

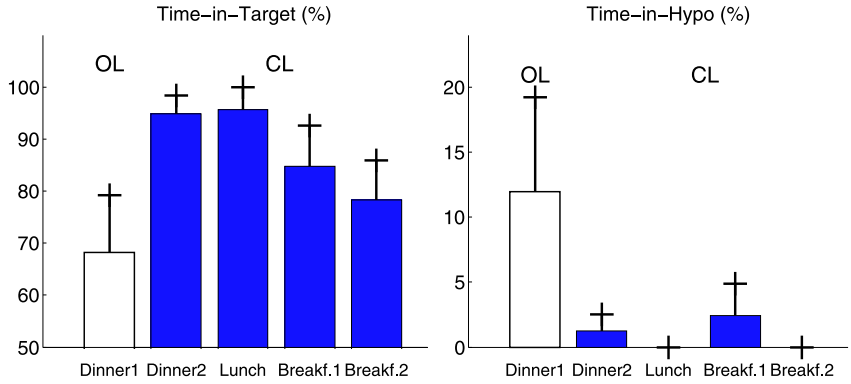
The study was not designed nor powered to statistically compare open-loop versus closed-loop, but certain post hoc comparisons for a preliminary assessment of effect size can be made.

Figure 1, *top panel*, shows the results of meal control: percent time-in-target (70–180 mg/dL, *top left*) and percent time-in-hypoglycemia ($<$70 mg/dL, *top right*) evaluated in the 4-h postprandial period of each meal of the study. Dinner closed-loop control was better than open-loop control of the same meal on the previous day: time-in-target increased from 68.17 to 94.84% and time-in-hypoglycemia was reduced ~10-fold (11.95 vs. 1.25%). Lunch average control achieved by closed-loop was similar to the one achieved at dinner. No hypoglycemia was observed after lunch (12:00–16:00).

Breakfast confirmed itself as the most difficult meal to control: both breakfasts had less time-in-target than dinner and lunch (84.80 and 78.27 vs. 94.84 and 95.68%, respectively). In the first day breakfast, time-in-hypoglycemia was slightly higher than after dinner and lunch (2.44 vs. 1.25 and 0%, respectively), while no hypoglycemia was observed after the second day breakfast.

A similar picture emerges from the other meal-related metrics, reported in the *bottom panel* of Fig. 1.

Overnight control was also better on closed-loop versus open-loop: time-in-target, 89.40 vs. 84.97%; time-in-tight-target (80–140



Other Meal-Related Outcomes

		Open Loop	Closed Loop			
Meal Index	**Unit**	**Dinner1**	**Dinner2**	**Lunch**	**Breakf.1**	**Breakf.2**
Mean glucose	(mg/dL)	140.5 ± 17.5	124.7 ± 10.3	137.2 ± 12.8	140.5 ± 11.6	156.4 ± 6.8
Carbohydrate intake	(g)	76.1 ± 3.0	75.7 ± 6.9	90.2 ± 10.3	40.3 ± 3.8	40.3 ± 3.8
Insulin bolus	(U)	5.0 ± 0.6	7.1 ± 0.9	8.9 ± 1.7	4.4 ± 0.7	4.6 ± 0.8
Starting glucose	(mg/dL)	135.6 ± 20.1	126.3 ± 12.5	132.8 ± 12.6	124.2 ± 11.7	128.3 ± 14.8
Glucose peak	(mg/dL)	194.3 ± 20.4	159.0 ± 10.3	166.3 ± 16.0	178.0 ± 15.7	190.1 ± 9.9
Glucose 4 h after meal	(mg/dL)	116.4 ± 19.8	130.3 ± 9.7	162.9 ± 16.0	143.3 ± 10.1	148.3 ±18.5
Prandial excursion	(mg/dL)	58.7 ± 25.3	32.8 ± 12.4	33.5 ± 16.8	53.8 ± 9.0	61.9 ± 16.7
AUC Hyper	(mg · h/dL)	34.2 ± 24.2	1.9 ± 1.9	4.3 ± 3.2	12.0 ± 8.2	12.3 ± 7.1
AUC Hypo	(mg · h/dL)	0.8 ± 0.4	0.1 ± 0.1	0.0 ± 0.0	0.4 ± 0.4	0.0 ± 0.0
HBGI	(·)	5.72 ± 2.04	1.97 ± 0.76	2.87 ± 1.11	4.13 ± 1.19	5.47 ± 1.02
LBGI	(·)	2.89 ± 1.16	1.13 ± 0.51	0.60 ± 0.49	1.16 ± 0.75	0.24 ± 0.11

Figure 1—Meal control achieved in the five meals of the study (the first dinner was handled in open-loop mode, and all other meals were handled by closed-loop). Time-in-target depicted on the *left*, time-in-hypoglycemia (hypo) on the *right*. Other meal-related outcomes are reported as mean ± SD. All metrics were evaluated in the postprandial period (i.e., 4 h after the meal) associated to each meal and based on continuous glucose monitoring sensor reading, suitably a posteriori processed to improve accuracy, as described in Beck et al. (11). Prandial excursion is defined as glucose peak minus starting glucose. AUC Hyper, area under the blood glucose curve above the hyperglycemia threshold (180 mg/dL); AUC Hypo, area under the blood glucose curve below the hypoglycemia threshold (70 mg/dL). HBGI and LBGI denote the high and low blood glucose indices, respectively (defined in Refs. 12,13). Breakf., breakfast; CL, closed-loop; OL, open-loop.

mg/dL), 59.07 vs. 48.53%; and time-in-hypoglycemia, 0.00 vs. 8.19%. Although the closed-loop was challenged with more meals than open-loop, in terms of overall performance, percent time-in-target was on average >75% with both treatments (82.05 open-loop vs. 84.66% closed-loop), and a sevenfold reduction of time-in-hypo was observed with closed-loop (8.56 open-loop vs. 1.15% closed-loop).

CONCLUSIONS

Effective postprandial glycemic control is one of the major challenges to AP systems based on subcutaneous insulin infusion. To respond to this challenge, we used a meal-informed MPC strategy. In this report, we provide data on the first wearable AP outpatient study based on meal-informed MPC, showing its ability to reduce postprandial glycemic excursions. These results confirm inpatient findings of the effectiveness of MPC-based strategies and pave the way to randomized crossover outpatient studies of longer duration. The encouraging results of this report for a single meal (dinner) control needs to be confirmed in future long-term randomized studies with numerous meals, proving sustained superiority of MPC versus the commonly used bolus calculator (as those provided by pumps or meter). Because improvements in the power handling of the mobile AP platform are needed for around-the-clock experiments, the initial step may have to follow a hybrid closed-loop mode (i.e., closed-loop treatment from dinner to wake-up time and standard open-loop therapy during daytime).

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Author Contributions. All authors reviewed and provided edits and comments on manuscript drafts. S.D.F. was the senior engineer responsible for the trial, design of the protocol, data analyses, and drafting of the manuscript. D.B. was the main study physician. F.D.P. was responsible for development of the control algorithm, implementation of the controller, and telemedicine function on the DiAs system. G.L. was responsible for development of the telemedicine system. R.V. was the engineer responsible for the trial and data analyses. A.F. and R.S. were study physicians. C.T. and M.M. were responsible for development of the control algorithm. S.S. was responsible for development of the telemedicine system. P.K.-H. was the chief engineer of the DiAs smartphone-based system and user interface. B.P.K. was principal investigator at the University of Virginia and responsible for development of the DiAs system, protocol design, and drafting of the manuscript. J.H.D. and E.R. were responsible for

the design of the protocol and drafting of the manuscript. L.M. was the principal investigator of the Pavia Unit and responsible for development of the algorithm and drafting of the manuscript. A.A. was chief of the metabolic diseases unit at Padova Hospital. C.C. is the principal investigator and responsible for the design of the protocol, data analysis, and drafting of the manuscript. C.C. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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