First Use of Model Predictive Control in Outpatient Wearable Artificial Pancreas

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...
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,
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
announcements, 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
malfuntioning 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
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. P.K.-H. was the chief investigator at the University of Virginia and was responsible for development of the control algorithm. S.S. was the engineer responsible for the trial and closed-loop development. 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

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**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.

- **Mean glucose (mg/dL)**: OL 140.5 ± 17.5 vs. CL 124.7 ± 10.3%
- **Carbohydrate intake (g)**: OL 76.1 ± 3.0 vs. CL 75.7 ± 6.9%
- **Insulin bolus (U)**: OL 5.0 ± 0.8 vs. CL 7.1 ± 0.9%
- **Starting glucose (mg/dL)**: OL 135.8 ± 20.1 vs. CL 126.3 ± 12.5%
- **Glucose peak (mg/dL)**: OL 194.3 ± 20.4 vs. CL 159.0 ± 10.3%
- **AUC Hyper (mg · h/dL)**: OL 34.2 ± 24.2 vs. CL 1.9 ± 1.9%
- **AUC Hypo (mg · h/dL)**: OL 0.8 ± 0.4 vs. CL 0.1 ± 0.1%
- **HBGI** (as glucose peak minus starting glucose): OL 7.2 ± 2.04 vs. CL 1.97 ± 0.76
- **LBGI** (as glucose peak minus starting glucose): OL 2.89 ± 1.16 vs. CL 1.13 ± 0.51

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**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
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.

References