ORIGINAL ARTICLE

Feasibility Study of a Bio-inspired Artificial Pancreas in Adults with Type 1 Diabetes

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Abstract

Background: This study assesses proof of concept and safety of a novel bio-inspired artificial pancreas (BiAP) system in adults with type 1 diabetes during fasting, overnight, and postprandial conditions. In contrast to existing glucose controllers in artificial pancreas systems, the BiAP uses a control algorithm based on a mathematical model of β -cell physiology. The algorithm is implemented on a miniature silicon microchip within a portable hand-held device that interfaces the components of the artificial pancreas.

Materials and Methods: In this nonrandomized open-label study each subject attended for a 6-h fasting study followed by a 13-h overnight and post-breakfast study on a separate occasion. During both study sessions the BiAP system was used, and microboluses of insulin were recommended every 5 min by the control algorithm according to subcutaneous sensor glucose levels. The primary outcome was percentage time spent in the glucose target range (3.9–10.0 mmol/L).

Results: Twenty subjects (55% male; mean [SD] age, 44 [10] years; duration of diabetes, 22 [12] years; glycosylated hemoglobin, 7.4% [0.7%] [57 (7) mmol/mol]; body mass index, 25 [4] kg/m²) participated in the fasting study, and the median (interquartile range) percentage time in target range was 98.0% (90.8–100.0%). Seventeen of these subjects then participated in the overnight/postprandial study, where 70.7% (63.9–77.4%) of time was spent in the target range and, reassuringly, 0.0% (0.0–2.3%) of time was spent in hypoglycemia (<3.9 mmol/L).

Conclusions: The BiAP achieves safe glycemic control during fasting, overnight, and postprandial conditions.

Introduction

FOR MANY PEOPLE WITH TYPE 1 diabetes mellitus (T1DM), achieving optimal glycemic control without recurrent hypoglycemia is a challenge. Severe or prolonged hypoglycemia is a major concern and can result in seizures or cardiac arrhythmias and may underlie the “dead-in-bed” syndrome.^{1,2} A closed-loop insulin delivery system, also referred to as an artificial pancreas, has the potential to improve glycemic control, reduce the incidence of hypoglycemia, and

improve quality of life. Several closed-loop insulin delivery devices have been developed and have shown encouraging results.^{3,4} However, further work is required to optimize the devices for use outside a controlled clinical environment.

The ideal artificial pancreas is one that replicates the physiology of the biological pancreas and more specifically the functions of the insulin secreting β -cells. Several recent mathematical models describing β -cell insulin release proportional to glucose concentration have been reported, enabling the implementation of β -cell physiology in a closed-loop

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This study is registered at ClinicalTrials.gov with clinical trial identification number NCT01534013.

Parts of this study were presented in abstract form at the Diabetes Technology Meeting, held in Bethesda, Maryland, November 8–10, 2012, at the Advanced Technologies & Treatments for Diabetes Meeting, held in Paris, France, February 28–March 2, 2013, and at the European Association for the Study of Diabetes Meeting, held in Barcelona, Spain, September 23–27, 2013.

The views expressed are those of the authors and not necessarily those of the Wellcome Trust, the National Health Service, the National Institute for Health Research, or the Department of Health.

insulin delivery system.^{5–7} The bio-inspired artificial pancreas (BiAP) is one such system that uses a novel control algorithm⁸ based on the mathematical model of the β -cell physiology proposed by Pedersen et al.⁵ and implemented using semiconductor microchip technology. This approach differs from existing glucose controllers evaluated in clinical closed-loop studies that are mainly based on classical control engineering techniques such as proportional integral derivative (PID) control with incorporation of cephalic phase response and insulin feedback, model predictive control, and fuzzy logic.^{9–14} The idea of using a bio-inspired approach for blood glucose control was first proposed in a physiological insulin delivery controller by Steil et al.,¹⁵ whereas others pursued a minimal model of insulin secretion for blood glucose control.¹⁶ The minimal model of insulin secretion was compared with the physiological insulin delivery controller, and although both were able to fit experimental data with a biphasic insulin release in response to varying glucose concentrations, the physiological controller was more stable under closed-loop conditions. In the first clinical closed-loop insulin delivery study, the physiological insulin delivery controller was used.¹⁷

Using a bio-inspired approach replicating the biphasic nature of insulin secretion by the β -cell may have clinical advantages, particularly when used with intraperitoneal insulin or with novel ultrarapid insulins. Furthermore, semiconductor microchip technology offers unique advantages of miniaturization and low power when designing bio-inspired systems that replicate physiology.¹⁸ Implementation of physiological processes in semiconductor technology has been successful in other areas, including cochlear implants for born-deaf children.¹⁹ The BiAP algorithm is implemented on a miniaturized low-power microchip to make a small hand-held medical device, whereas most studies to date with other controllers have used laptop computers.¹⁴ More recently, the feasibility of using a smartphone platform for the artificial pancreas system has been tested in an outpatient setting.²⁰

We have shown in silico that the bio-inspired glucose controller performs comparably with a published PID controller and in the adolescent population achieved an increased

time in the glucose target range and reduced risk index.²¹ A recent review has highlighted the potential advantages of using β -cell behavior in artificial pancreas systems.⁹

The algorithm

Figure 1 is a schematic diagram of the bio-inspired controller that has previously been published in detail.⁸ The core component of the bio-inspired glucose controller is the mathematical model of the β -cell physiology. In addition, it incorporates an insulin feedback term to avoid insulin stacking by compensating for delays associated with subcutaneous insulin delivery.²²

To attenuate the delays associated with subcutaneous glucose sensing, glucose measurements are forecasted 15 min ahead using a linear regression of the last six glucose values (i.e., the preceding 30 min). This linear regression is reset when the glucose sensor is recalibrated.

A personalized tuneable gain is used to overcome the intra- and intersubject variability in insulin sensitivity. The personalized tuneable gain is based on the individual subject's pre-experimental correction factor (CF). Using existing parameters from a cohort of virtual subjects ($n=30$) in the University of Virginia T1DM simulator we were able to demonstrate that the CF correlated well with the optimal gain for each individual in that cohort ($R^2=0.999$, $P<0.01$). In particular, the following nonlinear correlation between the two parameters was found: $K=0.751/CF$, where CF is in mmol/L per U. The CF range for the study population in the BiAP study was 1 unit of insulin to 1.0–4.0 mmol/L, which is translated into a gain range of 0.2–0.75 (arbitrary units).

The basal insulin term of the β -cell model used is set to 70% of the subject's basal insulin infusion profile.

The states of the ordinary differential equations making up the β -cell model are initialized based on the initial glucose measurement. These values are selected from a precalculated look-up table storing the ordinary differential equations' states values corresponding to different glucose concentrations.

To tackle the perturbation introduced by the meals, a meal announcement strategy is used consisting of giving 70% of

FIG. 1. Block diagram of the bio-inspired controller. CHO, carbohydrate; I:CHO, insulin:carbohydrate ratio; K, tuning gain; L.G.S., low glucose suspend; s.c. sensor, subcutaneous sensor; RRP, readily releasable pool; SR, secretion rate.

the insulin bolus calculated using the subject's carbohydrate-to-insulin ratio immediately before ingestion of the meal.

To minimize hypoglycemia, a low glucose suspend algorithm is incorporated on top of the controller. This low glucose suspend algorithm reduces the insulin delivery proposed by the controller to 50% if the forecasted glucose value falls below a predefined threshold and suspends the insulin delivery if it falls below a second lower predefined threshold. To prevent rebound hyperglycemia, the insulin suspension is limited to 90 min, after which time the insulin delivery is resumed to 50% for 30 min, and after this period total suspension is activated again if the hypoglycemic condition is satisfied. It is important to note that the low glucose suspend algorithm does not affect the meal bolus.

To avoid insulin stacking due to previous correction boluses administered before the start of the trial, the controller was not fully activated (only the basal insulin delivery and safety mechanism were initiated) until the drop in glucose level was less than a predefined threshold. Note that this measure was only used in the 13-h studies.

The control algorithm, implemented on a single miniature 5- $\times$ 5-mm silicon microchip within a portable hand-held device, receives glucose data from a subcutaneous sensor and controls insulin infusion rates via an insulin pump.

In this study, we have assessed the BiAP system in adults with T1DM for proof of concept and safety initially in fasting conditions, followed by overnight and postprandial studies.

Materials and Methods

This is a nonrandomized open-label prospective study. Regulatory approval from the regional ethics committee and Medicines and Healthcare Products Regulatory Agency was obtained. Subjects with T1DM were recruited from the diabetes clinics at Imperial College Healthcare NHS Trust in London, United Kingdom. Inclusion criteria were 18–75 years of age, duration of diabetes >1 year, fasting C-peptide level of <0.2 nmol/L, treatment with continuous subcutaneous insulin infusion for >6 months, and glycosylated hemoglobin (HbA1c) level of <8.5% (69 mmol/mol). Exclusion criteria were recurrent severe hypoglycemia, pregnancy or planning pregnancy, breastfeeding, enrollment in other clinical studies, and active malignancy or under investigation for malignancy. Informed written consent was obtained from each subject, and screening was performed.

Fasting (6-h) closed-loop study protocol

Subjects attended the NIHR/Wellcome Trust Imperial Clinical Research Facility at 08:00 h fasting. The capillary blood glucose level was measured on arrival to the research unit, and the subject's basal rate at that point was adjusted if deemed necessary by the attending physician from 08:00 h to 10:00 h. A subcutaneous glucose sensor (Enlite™; Medtronic, Northridge, CA) was inserted in the abdomen and connected to the hand-held unit containing the control algorithm, which in turn was connected to a laptop with a graphical user interface implemented in MATLAB™ (MathWorks®, Natick, MA), allowing the study team to approve each recommended insulin dose. The control algorithm was tuned proportionally to the subject's insulin sensitivity factor (the reduction in glucose concentration by 1 unit of insulin), aiming for a target glucose of 5.5 mmol/L.

The subject's own insulin pump was replaced with the study pump (ACCU-CHEK® Spirit Combo pump; Roche, Basel, Switzerland), and their usual basal insulin rates were continued subcutaneously until closed-loop insulin delivery was commenced. Rapid-acting insulin aspart (Novorapid®; Novo Nordisk, Bagsværd, Denmark) was used throughout the study. The sensor signal was transmitted to the hand-held unit by cable, and communication between the hand-held unit and the laptop was achieved via USB. The insulin infusion instruction was transmitted to the pump by the Roche Bluetooth® (Bluetooth SIG, Kirkland, WA) communication protocol. Following sensor calibration to venous glucose at the start of closed-loop control, the control algorithm recommended an insulin dose according to the interstitial glucose level measured by the subcutaneous sensor every 5 min. Every 15 min throughout the study, a venous blood sample was taken and analyzed for glucose using the YSI 2300 glucose and lactate analyzer (Yellow Springs Instrument, Yellow Springs, OH). Subjects were allowed to drink water throughout the study.

Overnight and post-breakfast (13-h) closed-loop study protocol

Subjects attended the NIHR/Wellcome Trust Imperial Clinical Research Facility nonfasting at 18:00 h and consumed a meal of their choice. They were advised to take their normal insulin bolus prior to meal consumption. The closed-loop insulin delivery system was set up and connected as outlined for the 6-h fasting study except that communication between the hand-held unit and the laptop was achieved via Bluetooth radio, allowing subjects to be mobile. A slightly higher target glucose level of 6.5 mmol/L was used for increased safety during the overnight period. Following sensor calibration to venous glucose at the start of closed-loop control at 22:00 h, the control algorithm recommended an insulin dose according to the interstitial glucose level measured by the subcutaneous sensor every 5 min. Every 15–30 min throughout the study, a venous blood sample was taken and analyzed for glucose using the YSI 2300 glucose and lactate analyzer. Subjects drank only water overnight. At 06:00 h the next day a standard breakfast containing 40 g of carbohydrates was provided. The meal was announced to the algorithm, and a 70% bolus dose of insulin, calculated using the subject's insulin:carbohydrate ratio (the amount of carbohydrates that 1 unit of insulin will cover), was delivered. The closed-loop study ended 5 h after the meal, at 11:00 h.

For both phases of the study the primary outcome was percentage time spent in the glucose target range of 3.9–10.0 mmol/L. Secondary outcomes were percentage time in euglycemia (3.9–7.8 mmol/L), hypoglycemia (<3.9 mmol/L), and hyperglycemia (>10.0 mmol/L). Other secondary outcomes were mean glucose level, insulin dose (in units/hour), and glycemic variability measures of Low Blood Glucose Index (LBGI) (reference range, 0.0–6.9) and High Blood Glucose Index (HBGI) (0.0–7.7).^{23,24} Data were analyzed using SPSS version 20 software (IBM, Armonk, NY).

Results

Twenty adult subjects with T1DM (55% male; mean [SD] age, 44 [10] years; duration of diabetes, 22 [12] years; duration of insulin pump therapy, 3.4 [4] years; HbA1c, 7.4%

TABLE 1. GLYCEMIC OUTCOME MEASURES FROM THE FASTING CLOSED-LOOP STUDY

Outcome measure	Results (n=20)	
	Sensor glucose	Blood glucose
Time 12:00–16:00 h (total 4 h)		
% time in		
Target range (3.9–10.0 mmol/L)	98.0 (90.8–100.0)	100.0 (84.7–100.0)
Euglycemia (3.9–7.8 mmol/L)	96.4 (63.7–100.0)	100.0 (75.0–100.0)
Hypoglycemia (<3.9 mmol/L)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
Hyperglycemia (>10.0 mmol/L)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
Glucose (mmol/L)	5.7 (1.8)	5.8 (1.5)
Low Blood Glucose Index (0.0–6.9)	3.2 (4.1)	2.4 (2.0)
High Blood Glucose Index (0.0–7.7)	1.4 (3.5)	1.1 (2.2)
Time 10:00–16:00 h (total 6 h)		
% time in		
Target range (3.9–10.0 mmol/L)	89.0 (69.1–98.7)	86.5 (78.4–100.0)
Euglycemia (3.9–7.8 mmol/L)	69.9 (49.8–91.1)	72.0 (53.6–89.0)
Hypoglycemia (<3.9 mmol/L)	0.0 (0.0–5.8)	0.0 (0.0–1.0)
Hyperglycemia (>10.0 mmol/L)	0.8 (0.0–17.8)	0.0 (0.0–17.2)
Glucose (mmol/L)	6.6 (1.9)	6.7 (1.6)
Low Blood Glucose Index (0.0–6.9)	3.0 (3.6)	2.4 (1.9)
High Blood Glucose Index (0.0–7.7)	3.9 (4.5)	3.6 (3.2)

Data are median (interquartile range) values or mean (SD) values as indicated.

[0.7%]; body mass index, 25 [4] kg/m²) participated in the 6-h fasting closed-loop study. Of these, 17 subjects then took part in the 13-h overnight and postprandial study (one subject attended for the study visit, but the study had to be discontinued because of a fault with the insulin infusion cannula and was therefore excluded from the data analysis, and two subjects withdrew from the study).

Closed-loop control during fasting conditions

The glycemic outcome measures from the fasting 6-h closed-loop study are summarized in Table 1. The glucose

data from the first 2 h of the study have been excluded from the primary data analysis as the controller is unable to influence the glucose concentration over this initial time period. Additionally, all data points over the 6-h study are reported, to illustrate that the controller is able to bring the glucose level down to target safely irrespective of the initial conditions. It is reassuring that no time was spent in severe hyperglycemia (>15 mmol/L) or severe hypoglycemia (<2.8 mmol/L). The mean (SD) sensor glucose from the fasting study was 5.7 (1.8) mmol/L with a 95% confidence interval of 4.9–6.5 mmol/L. The target glucose level of 5.5 mmol/L lies within this confidence interval, and we are

TABLE 2. GLYCEMIC OUTCOME MEASURES FROM THE OVERNIGHT AND POSTPRANDIAL CLOSED-LOOP STUDY (00:00 H–11:00 H) AND FROM THE OVERNIGHT PERIOD ONLY (00:00 H–06:00 H)

Outcome measure	Results (n=17)	
	Sensor glucose	Blood glucose
Time 00:00–11:00 h (11 h in total)		
% time in		
Target range (3.9–10.0 mmol/L)	70.7 (63.9–77.4)	67.6 (59.5–70.3)
Euglycemia (3.9–7.8 mmol/L)	42.9 (18.8–51.9)	37.8 (29.7–51.4)
Hypoglycemia (<3.9 mmol/L)	0.0 (0.0–2.3)	0.0 (0.0–0.0)
Hyperglycemia (>10.0 mmol/L)	26.3 (20.3–26.3)	32.4 (29.7–40.5)
Glucose (mmol/L)	8.3 (1.2)	9.0 (1.4)
Low Blood Glucose Index (0.0–6.9)	3.0 (5.1)	1.2 (1.9)
High Blood Glucose Index (0.0–7.7)	8.3 (3.3)	8.3 (3.4)
Time 00:00–06:00 h (6 h in total)		
% time in		
Target range (3.9–10.0 mmol/L)	93.2 (71.6–97.3)	100 (81.3–100)
Euglycemia (3.9–7.8 mmol/L)	67.6 (32.4–82.4)	58.8 (35.3–94.1)
Hypoglycemia (<3.9 mmol/L)	0.0 (0.0–4.1)	0.0 (0.0–0.0)
Hyperglycemia (>10.0 mmol/L)	0.0 (0.0–14.9)	0.0 (0.0–11.8)
Glucose (mmol/L)	6.7 (1.9)	7.4 (2.0)
Low Blood Glucose Index (0.0–6.9)	3.0 (5.1)	1.2 (1.9)
High Blood Glucose Index (0.0–7.7)	3.2 (2.8)	3.4 (3.9)

Data are median (interquartile range) values or mean (SD) values as indicated.

FIG. 2. Median glucose trend and insulin delivered for all 20 subjects during the 6-h fasting closed-loop study. Red dotted line = median blood (YSI) glucose ($\pm$ interquartile range); red dashed lines = 5th and 95th percentiles for blood glucose; blue triangle line = median sensor glucose ($\pm$ interquartile range); orange bars = mean insulin dose delivered; black dashed lines = upper/lower glucose target thresholds.

therefore confident that the mean glucose level achieved did not differ significantly from the target. Figure 2 displays the median sensor and blood glucose concentration with interquartile ranges (IQRs) throughout the 6-h study. The glycemic outcome measures based on sensor glucose were equivalent to the blood glucose measurements, suggesting good sensor accuracy. The median absolute relative difference (MARD) between the venous blood glucose level and the sensor glucose level was 9.5 (IQR 4.9–18.0%) for all subjects. The sensor was recalibrated on six occasions overall during a total of 120 h of closed-loop control (0.3 recalibrations/6-h study). The controller's insulin dose recommendations were rejected on eight occasions overall, representing 0.6% of all recommended doses. The rejected insulin dose recommendations were a result of intermittent artifactual glucose spikes reported by the sensor in two subjects. During the 6 h of the study the low glucose suspend (either 50% reduction or complete suspension in insulin delivery) feature came into play on 10 occasions overall (2.0 times/24-h day).

Closed-loop control during the night and postprandially

Table 2 summarizes the glycemic outcome measures from the combined overnight and postprandial closed-loop study and the glycemic outcome measures from the night period only. The data generated from the first 2 h of closed-loop control were excluded from the analysis to account for the insulin bolus taken with the evening meal at 18:00 h, making the assumption that the average insulin action time is up to 6 h. The median sensor and blood glucose levels with IQRs throughout the whole 13-h study period are displayed in

Figure 3. The mean glucose level remains within the target from closed-loop start at 22:00 h until breakfast at 06:00 h, and the mean postprandial peak glucose level reaches 12.0 mmol/L before returning to target. The sensor glucose 95% confidence interval for the overnight study was 5.8–7.6 mmol/L with a mean (SD) of 6.7 (1.9) mmol/L. The achieved mean glucose overnight level did not differ significantly from the target glucose level of 6.5 mmol/L as the target value lies within the confidence interval.

The MARD between the venous blood glucose and the sensor glucose was 11.8% (5.4–20.9%) for all subjects. The sensor was recalibrated on 21 occasions overall during a total of 221 h of closed-loop control (1.6 recalibrations/13-h study). The controller's insulin dose recommendations were adhered to at all times. The low glucose suspend feature was activated on 12 occasions overall (1.3 times/24-h day).

Discussion

The results from our study demonstrate the feasibility and safety of the BiAP and its ability to achieve glycemic control in adults with T1DM. This is the first time the bio-inspired control algorithm has been evaluated in human subjects with T1DM and confirms the conclusions from *in silico* studies with virtual subjects in a simulated environment.⁸ This is a feasibility study and at this stage is limited by the absence of a control group. The primary outcome of the fasting study, 98.0% of time spent in target range (3.9–10.0 mmol/L) and 96.4% in a tighter target (3.9–7.8 mmol/L), is comparable to that of other closed-loop fasting studies.^{14,17,25} The inclusion of the glucose data from the first 2 h of the study in the

FIG. 3. Median glucose trend and insulin delivered for all 17 subjects during the 13-h overnight and postprandial closed-loop study. Red dotted line = median blood (YSI) glucose ($\pm$ interquartile range); red dashed lines = 5th and 95th percentiles for blood glucose; blue triangle line = median sensor glucose ($\pm$ interquartile range); orange bars = mean insulin dose delivered; black dashed lines = upper/lower glucose target thresholds. A standard breakfast meal containing 40 g of carbohydrates was provided at 06:00 h and announced to the algorithm.

subanalysis, showing 89% within the target range, demonstrated that the controller was able to safely bring down the glucose level to target irrespective of the blood glucose level at initialization of the controller and in a scenario where the controller does not know the insulin on board. We advised subjects to avoid exercise for 24 h prior to the study, so the higher initial fasting blood glucose level on arrival may in part be a result of reduced activity the evening before the study. Hypoglycemia (glucose level <3.9 mmol/L) occurred in only one subject, and there were no episodes of severe hypoglycemia. To solve the issue of artifactual sensor spikes leading to inappropriate insulin infusion rates, saturation thresholds for glucose rate of change were introduced into the control algorithm, avoiding excess insulin infusion.

The overall results from the 6-h fasting study confirmed the safety of the BiAP system, allowing further assessment over a longer period of time and following a meal during which the overall time in target range was acceptable at 71%. There is scope to further optimize the glucose controller to allow more aggressive glucose lowering when concentrations are above the hyperglycemic threshold, particularly postprandially. We observed that the insulin feedback term was exerting a significant influence after a meal bolus, and we aim to address this in the next stage of the study. With the current glucose sensing technology and insulin analogs available, providing the facility to announce meals, in order to minimize prandial hyperglycemia and delayed postprandial hypoglycemia, seems to be the best approach. However, proving safety of any artificial pancreas algorithm in the

absence of meal announcement is important, and this will also be assessed in the next stage of the BiAP study.

Differences in study protocol preclude comparisons with other nonfasting closed-loop studies, but the inclusion of a longer postprandial period would have allowed a further reduction of the postprandial glucose level to be demonstrated. As a result of the postprandial glucose surge, the mean HBGI was elevated at 8.3 mmol/L. The median peak postprandial sensor glucose level was, however, reasonable at 12.0 mmol/L, and target mean glucose level was achieved during overnight control. It is reassuring that the LBG1 was low at 3.0 mmol/L, suggesting minimal risk of hypoglycemia, although the condition was not completely eliminated. The addition of glucagon in a bihormonal closed-loop system has the potential to reduce the incidence hypoglycemia further.^{26–28}

It has been reported that glucose sensors are least accurate on the first day of operation.²⁹ A MARD of 9.5% and 11.8% as seen in the fasting and overnight/postprandial study, respectively, suggests acceptable sensor accuracy, although the MARD may be biased by the number of recalibrations in any assessment of a closed-loop system.

It is important to point out that the β -cell model used in our system is different than that used in PID controllers. The main difference between the two models lies in their structure. The β -cell model used in our controller⁵ is a deductive model, describing the mechanistic events of insulin secretion at a subcellular level (including mobilization, docking, fusion, and kiss-and-run exocytosis). In contrast, PID is an inductive

model, in which structure and parameters do not have a physiological meaning.

Although both models are able to replicate the insulin secretion behavior of the β -cell observed in in vitro studies (with glucose step response, ramp, and staircase), with the PID model we were not able to replicate the reported response to a meal challenge.⁵ Another interesting feature observed in the mathematical model of β -cell physiology of Pedersen et al.⁵ is its intrinsic ability to filter the input noise that is not present in PID.

Administration of insulin subcutaneously poses a challenge to any artificial pancreas system due to delays and variability in absorption. To overcome these factors, intraperitoneal insulin delivery is being integrated into artificial pancreas systems, and physiological control algorithms in this scenario have significant potential to mimic non-diabetes β -cell responses.³⁰

Medical device usability and acceptability are significant factors for the design of any artificial pancreas system. In our BiAP system, the algorithm has been implemented in a microchip within a miniaturized low-power device, which makes it potentially suitable for integration with current insulin pumps and continuous glucose monitoring devices.

In conclusion, we have demonstrated safe glucose control using a novel implementation of β -cell physiology in a low-power microchip implemented in a portable hand-held device for closed-loop insulin delivery in subjects with T1DM fasting, overnight, and postprandially.

Acknowledgments

This article presents independent research funded by the Wellcome Trust and carried out at the NIHR/Wellcome Trust Imperial Clinical Research Facility. Imperial College London is supported by the NIHR Diabetes Research Network and the Imperial NIHR Biomedical Research Centre.

Author Disclosure Statement

No competing financial interests exist.

M.R. conducted the clinical trials, analyzed the data, contributed towards the design of the study, and wrote the manuscript. P.H. developed the control algorithm used, provided technical support during clinical trials, and reviewed and edited the manuscript. M.E.S. developed the electronics and provided technical support during clinical studies. P.P. provided technical support during the clinical trials. N.J. and H.T. conducted the clinical trials. D.P. conducted laboratory measurements of blood samples from the clinical trials. C.T. is the Principal Investigator and co-inventor of the project. D.J. designed the study and reviewed and edited the manuscript. P.G. invented the bio-inspired artificial pancreas, developed the electronics, and reviewed and edited the manuscript. N.O. designed the study and reviewed and edited the manuscript. N.O. 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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