Journal of Cystic Fibrosis 19 (2020) 159–161

Contents lists available at ScienceDirect

Journal of Cystic Fibrosis

journal homepage: www.elsevier.com/locate/jcf

Short Communication

Automated glycemic control with the bionic pancreas in cystic fibrosis-related diabetes: A pilot study

Jordan S. Sherwood[a], Rabab Z. Jafri[a], Courtney A. Balliro[a], Hui Zheng[b], Firas H. El-Khatib[c], Edward R. Damiano[c], Steven J. Russell[a], Melissa S. Putman[a,d,*]

[a] Diabetes Research Unit, Massachusetts General Hospital, Boston, MA, United States of America
[b] Biostatics Center, Massachusetts General Hospital, Boston, MA, United States of America
[c] Department of Biomedical Engineering, Boston University
[d] Department of Endocrinology, Boston Children's Hospital, Boston, MA, United States of America

ARTICLE INFO

Article history:
Received 1 February 2019
Revised 26 July 2019
Accepted 4 August 2019
Available online 13 August 2019

Keywords:
Cystic fibrosis
Cystic fibrosis-related diabetes
Bionic pancreas
Insulin
Glucagon
Automated glycemic control
Closed loop
Continuous glucose monitor

ABSTRACT

Cystic fibrosis-related diabetes (CFRD) is the most common extrapulmonary manifestation of cystic fibrosis. The current standard of care for CFRD involves treatment with insulin, typically via multiple daily injections. We conducted a small pilot study comparing usual care with automated glycemic control using the bihormonal (insulin and glucagon) and insulin-only configurations of the bionic pancreas. Both configurations of the bionic pancreas achieved good glycemic control, with mean glucose levels <150 mg/dl and minimal hypoglycemia. Subjects reported improved treatment satisfaction and reduced burden of diabetes management with the bionic pancreas. Further investigation of automated glycemic control in the treatment of CFRD is warranted.

1. Introduction

Cystic fibrosis-related diabetes (CFRD) affects approximately 20% of adolescents and up to 50% of adults with cystic fibrosis (CF) [1,2]. The development of CFRD is associated with decline in pulmonary function, compromised nutritional status, and increased mortality [3–6]. Treatment with insulin is associated with improved clinical status and decreased mortality [5,7,8]. CF carries a high treatment burden, and the development of CFRD adds to the complexity of care. Diabetes technologies such as continuous glucose monitoring (CGM) and insulin pump therapy are not frequently utilized in this patient population, although small studies show that they may be beneficial [9,10]. We have developed and studied an automated glucose control system – the bionic pancreas (BP) – that was primarily designed with the goal of improving glycemic control in those with type 1 diabetes (T1D). This device employs CGM coupled with mathematical algorithms that command a pump to automatically administer insulin and, in the bihormonal configuration, glucagon. In patients with T1D the bihormonal BP (BHBP) simultaneously lowers mean CGM glucose (CGMG) and time spent in hypoglycemic ranges, while the insulin-only BP (IOBP) decreased mean CGMG without increasing hypoglycemia [11–18]. Here, we examined the feasibility of automated glycemic control utilizing the BP in subjects with CFRD.

2. Materials and methods

We performed a three-arm, random-order, cross-over, pilot study consecutively comparing the BHBP, IOBP, and usual care (UC), each for one week without a washout period, in three subjects with CFRD. Inclusion criteria required that subjects be ≥18 years old with a clinical diagnosis of CFRD managed with a total daily dose (TDD) of insulin ≥0.1 u/kg/day. This TDD minimum was chosen to ensure subjects with a broad range of insulin requirements were included. Subjects were excluded if they had a diagnosis of liver failure or cirrhosis, renal failure on dialysis, history of lung or liver transplant, or exacerbation of pulmonary disease requiring hospitalization, or treatment with IV antibiotics within the past four weeks. The BP consisted of an iPhone 6S (Apple, Cupertino, CA, USA) running a mathematical dosing algorithm as previously described [11], identical to that used in T1D subjects without any modifications, that obtained glucose data from a Dexcom G5

* Corresponding author.
E-mail address: msputman@partners.org (M.S. Putman).

https://doi.org/10.1016/j.jcf.2019.08.002
1569-1993/

Table 1
Baseline characteristics

Subject	Age (years)	Sex	BMI (kg/m2)	Duration of CFRD (years)	Usual Care Insulin administration	Total daily dose insulin (u/kg/day)	Current use of CGM
1	25	F	18.8	16	MDI	0.96	No
2	32	F	20.4	18	CSII	0.71	No
3	32	F	22.2	0.7	MDI	0.19	No

CGM (Dexcom, San Diego, CA, USA). The BP could deliver subcutaneous doses of insulin and/or glucagon up to every 5 min via t:slim pumps (Tandem Diabetes Care, San Diego, CA, USA). The glucose target was set at 110 mg/dl for the BHBP and at 120 mg/dl for the IOBP. There were no restrictions on activity and subjects continued their normal diet, exercise, and work throughout the study. The BP was initialized only with subject body mass, without any information regarding their usual insulin regimen. Carbohydrate counting is eliminated with the BP, but subjects could utilize an integrated, optional meal announcement through the BP's user interface that only requires subjects to specify if the carbohydrate content of the meal is typical, tiny, small, or large for them. The insulin infusion set and cartridge were changed every other day. During the BHBP arm subjects reconstituted glucagon from an emergency glucagon kit (Lilly, Indianapolis, IN, USA) and changed the glucagon infusion set and cartridge daily. Subjects were remotely monitored for hypoglycemia during all three study arms and were contacted by study staff if they had a CGMG reading <50 mg/dl for >15 min. The co-primary outcomes were mean CGMG and % of time <54 mg/dl (3 mmol/L) on days 3–7 of each study arm (days 1–2 of each arm were excluded to allow for wash-out of long-acting insulin and initial adaptation of the BP algorithm). Given the preliminary nature of the study, only descriptive statistics are reported for the group.

3. Results

Subject characteristics are presented in Table 1. As part of their usual care, one subject used an insulin pump and none of the subjects used a CGM. Insulin total daily doses were 0.19, 0.71, and 0.96 u/kg/day. The group mean CGMG was nominally lower in both the BHBP (139 ± 15 mg/dl) and IOBP (149 ± 10 mg/dl) arms relative to UC (159 ± 35 mg/dl) (Fig. 1 and Table 2). Time in range (70–180 mg/dl) was nominally improved in the BP arms as was glucose variability, as demonstrated by smaller mean glucose standard deviation. During the BHBP arm, three subjects achieved a mean CGMG <154 mg/dl (predicted to be associated with a hemoglobin A1C under the ADA target of 7.0%), compared to two subjects during the IOBP arm and one subject during UC arm. The percentage of time <54 mg/dl was low in all three arms (0.2, 0.5, and 0.3%, respectively) without statistically significant differences between arms for any subject ($p \geq .45$) according to time series analysis. The percentage of time with CGMG 70–180 mg/dl was nominally increased in both the BHBP (80 ± 10%) and IOBP (76 ± 9%) arms compared to the UC arm (62 ± 23%). The percentage of time >250 mg/dl was nominally decreased in both the BHBP (4%) and the IOBP (5%) arms compared to UC (9%). During BP arms subjects used the meal announcement feature on average less than once per day. No subject endorsed nausea or vomiting on daily surveys while receiving glucagon during the BHBP arm. Survey data suggested that subjects had a decreased diabetes-management burden with the BP, spent less time thinking about their diabetes, felt freer with food choices, and had overall greater peace of mind.

Table 2
Summary of glycemic outcomes.

	BHBP	IOBP	UC
CGM glucose (mg/dl)	139 ± 15 (122–151)	149 ± 10 (137–157)	159 ± 35 (124–194)
Time <54 mg/dl (%)	0.2 ± 0.2 (0–0.4)	0.5 ± 0.1 (0.4–0.5)	0.3 ± 0.3 (0–0.6)
Time <60 mg/dl (%)	0.5 ± 0.6 (0–1.1)	0.8 ± 0.5 (0.5–1.4)	0.7 ± 0.4 (0.2–1.0)
Time 70–180 mg/dl (%)	80 ± 10 (73–91)	76 ± 9 (71–87)	62 ± 23 (37–83)
Time >250 mg/dl (%)	4 ± 4 (0.1–8)	5 ± 2 (2–6)	9 ± 7 (2–16)
Predicted A1c based on mean CGMG (%)	6.5 ± 0.5 (5.9–6.9)	6.8 ± 0.4 (6.4–7.1)	7.2 ± 1.2 (6.0–8.4)

Outpatient data ($n = 3$) based on CGM data obtained every 5 min. Presented as mean $\pm$ SD (range).

4. Discussion

This pilot study suggests that glycemic control with the BP is worthy of further investigation in patients with CFRD.

Several features of the BP address unique challenges in the management of CFRD. The BP automatically and continuously adapts to a wide range of insulin needs, a useful attribute given the day-to-day fluctuations in insulin requirements that are common in CFRD. Additionally, maintaining adequate nutrition is

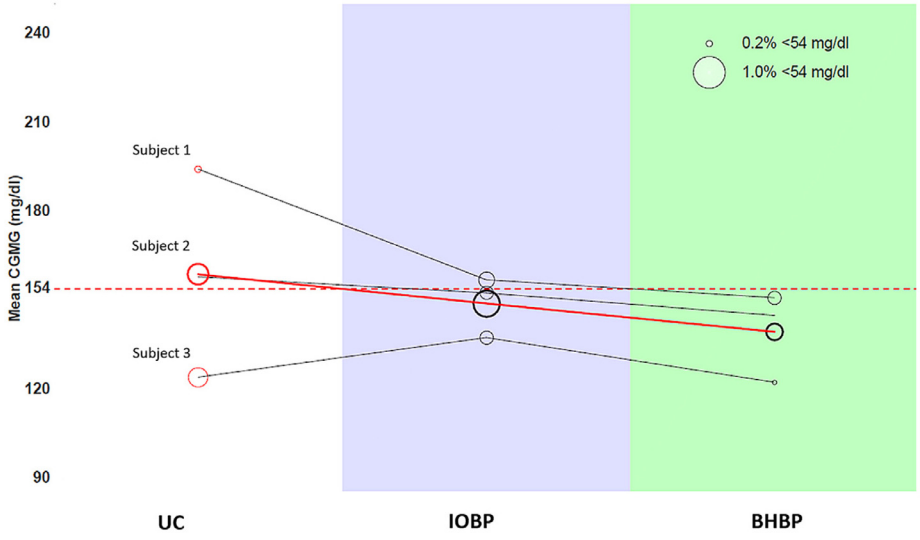

Fig. 1. Distributions of Mean Glucose Levels and Hypoglycemia. Distribution of mean CGM glucose levels and hypoglycemia in the UC, IOBP and BHBP arms. Mean CGM glucose levels for each participant in each arm (shown as circles) are connected by black lines. For each participant, the circle diameter is proportional to the percentage of CGM glucose values <54 mg/dl. The heavy circles and heavy red line represent the group means. The horizontal red dashed line refers to the glucose level corresponding to the ADA therapy goal of 154 mg/dl (HbA1c <7%). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

essential in CF, and patients typically consume a high-calorie diet with frequent snacks. Meal announcements to the BP are optional and do not require carbohydrate counting. If meal announcements are not issued, the BP will automatically increase insulin delivery to return the glucose to target range. In this pilot study, subjects mostly did not use the meal announce option, but rather chose to rely on fully automated glycemic control. Eliminating carbohydrate counting can greatly decrease patient burden.

In addition to diminished capacity for insulin secretion, CFRD patients also have decreased glucagon secretory capacity, which can increase the risk of hypoglycemia [19,20]. The BHBP may ameliorate hypoglycemia by compensating for the reduced counter-regulatory capacity in CFRD. In this study, good glucose control was achieved with both BHBP and IOBP, and hypoglycemia was minimal. The BP algorithm was not modified for testing in this new population and was able to adapt to subjects with long-standing diabetes duration and high baseline insulin requirements (subjects 1 and 2) as well as a subject with minimal insulin requirements (subject 3) without an increase in hypoglycemia. A larger study will be required to determine whether the IOBP or BHBP configuration will be optimal for patients with CFRD or if any modifications to the algorithm may be warranted to address unique aspects of CFRD.

Better glycemic control could decrease morbidity and mortality in this patient population. Additionally, burdensome tasks of diabetes, including frequent insulin injections, multiple fingerstick glucose checks, and close monitoring of carbohydrate intake, are all minimized with the BP relative to other approaches to diabetes management. This could reduce burden of disease management associated with CF and improve quality of life even apart from effects on glycemic control. Based on these preliminary results, larger-scale studies are justified to investigate the safety and efficacy of the BP in people with CFRD.

Acknowledgments

This study was supported by donations by private individuals to the Bionic Pancreas Project at Massachusetts General Hospital and Boston University, by NIH R01DK119699-01, and by startup funds to M.S.P. J.S.S. received funding from NIH training T32 DK007028. J.S.S., C.B., S.J.R., and M.S.P. designed the study and interpreted the data. F.H.K. and E.R.D. designed and built the closed-loop control algorithm and bionic pancreas system. S.J.R. supervised the human studies. H.Z. and F.H.K. performed the statistical analysis. J.S.S. wrote the first draft of the manuscript. J.S.S. C.B., R.Z.J., F.H.K., E.R.D., S.J.R, and M.S.P. participated in revision of the manuscript for important intellectual content. S.J.R. and M.S.P. had full access to the data and take full responsibility for this work as a whole, including the study design and the decision to submit and publish the manuscript.

The authors thank the volunteers for their time and enthusiasm; Mary Larkin, Camille Collings, Nancy Kingori, Stephanie Dimodica, Khadija Tlaiti, Diabetes Research Center, MGH, for organizational and logistical support; Nancy Wei, Kerry Grennan and Takara Stanley for serving on the data safety and monitoring board for the study; and the members of the Partners Human Research Committee.

References

[1] Registry CFFP. Annual data report Bethesda. Maryland: Cystic Fibrosis Foundation; 2018.

[2] American Diabetes A. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2018. Diabetes Care 2018;41(Suppl. 1):S13–27. Epub 2017/12/10 https://doi.org/10.2337/dc18-S002. [PubMed PMID: 29222373].

[3] Milla CE, Warwick WJ, Moran A . Trends in pulmonary function in patients with cystic fibrosis correlate with the degree of glucose intolerance at baseline. Am J Respir Crit Care Med 2000;162(3):891–5. doi:10.1164/ajrccm.162.3.9904075. Pt 1. [PubMed PMID: 10988101].

[4] White H, Pollard K, Etherington C, Clifton I, Morton AM, Owen D, et al. Nutritional decline in cystic fibrosis related diabetes: the effect of intensive nutritional intervention. J Cyst Fibros 2009;8(3):179–85. doi:10.1016/j.jcf.2008.12.002. [PubMed PMID: 19179122].

[5] Moran A, Dunitz J, Nathan B, Saeed A, Holme B, Thomas W . Cystic fibrosis-related diabetes: current trends in prevalence, incidence, and mortality. Diabetes Care 2009;32(9):1626–31. doi:10.2337/dc09-0586. [PubMed PMID: 19542209 PMCID: 2732133].

[6] Lewis C, Blackman SM, Nelson A, Oberdorfer E, Wells D, Dunitz J, et al. Diabetes-related mortality in adults with cystic fibrosis. Role of genotype and sex. Am J Respir Crit Care Med 2015;191(2):194–200. doi:10.1164/rccm.201403-0576OC. [PubMed PMID: 25479583; PMCID: 4347432].

[7] Moran A, Pekow P, Grover P, Zorn M, Slovis B, Pilewski J, et al. Insulin therapy to improve BMI in cystic fibrosis-related diabetes without fasting hyperglycemia: results of the cystic fibrosis related diabetes therapy trial. Diabetes Care 2009;32(10):1783–8. doi:10.2337/dc09-0585. [PubMed PMID: 19592632; PMCID: 2752940].

[8] Mozzillo E, Franzese A, Valerio G, Sepe A, De Simone I, Mazzarella G, et al. One-year glargine treatment can improve the course of lung disease in children and adolescents with cystic fibrosis and early glucose derangements. Pediatr Diabetes 2009;10(3):162–7. doi:10.1111/j.1399-5448.2008.00451.x. [PubMed PMID: 19207231].

[9] Scheuing N, Badenhoop K, Borkenstein M, Konrad K, Lilienthal E, Laubner K, et al. German/Austrian Diabetes Prospective Documentation I. Why is insulin pump treatment rarely used in adolescents and young adults with cystic fibrosis-related diabetes? Pediatr Diabetes 2015;16(1):10–15. Epub 2014/07/06 https://doi.org/10.1111/pedi.12158. [PubMed PMID: 24984902].

[10] Frost F, Dyce P, Nazareth D, Malone V, Walshaw MJ. Continuous glucose monitoring guided insulin therapy is associated with improved clinical outcomes in cystic fibrosis-related diabetes. J Cyst Fibros 2018 Epub 2018/06/11. doi:10.1016/j.jcf.2018.05.005. [PubMed PMID: 29885744].

[11] El-Khatib FH, Russell SJ, Nathan DM, Sutherlin RG, Damiano ER. A bihormonal closed-loop artificial pancreas for type 1 diabetes. Sci Transl Med 2010;2(27) 27ra.. doi:10.1126/scitranslmed.3000619. [PubMed PMID: 20393188; PMCID: PMC4242106].

[12] Russell SJ, El-Khatib FH, Nathan DM, Magyar KL, Jiang J, Damiano ER . Blood glucose control in type 1 diabetes with a bihormonal bionic endocrine pancreas. Diabetes Care 2012;35(11):2148–55. doi:10.2337/dc12-0071. [PubMed PMID: 22923666; PMCID: 3476884].

[13] El-Khatib FH, Russell SJ, Magyar KL, Sinha M, McKeon K, Nathan DM, et al. Autonomous and continuous adaptation of a bihormonal bionic pancreas in adults and adolescents with type 1 diabetes. J Clin Endocrinol Metab 2014;99(5):1701–11. doi:10.1210/jc.2013-4151. [PubMed PMID: 24483160; PMCID: 4010702].

[14] Russell SJ, El-Khatib FH, Sinha M, Magyar KL, McKeon K, Goergen LG, et al. Outpatient glycemic control with a bionic pancreas in type 1 diabetes. N Engl J Med 2014;371(4):313–25. doi:10.1056/NEJMoa1314474. [PubMed PMID: 24931572; PMCID: 4183762].

[15] Russell SJ, Hillard MA, Balliro C, Magyar KL, Selagamsetty R, Sinha M, et al. Day and night glycaemic control with a bionic pancreas versus conventional insulin pump therapy in preadolescent children with type 1 diabetes: a randomised crossover trial. Lancet Diabetes Endocrinol 2016;4(3):233–43. Epub 2016/02/07 https://doi.org/10.1016/S2213-8587(15)00489-1. [PubMed PMID: 26850709; PMCID: PMC4799495].

[16] El-Khatib FH, Balliro C, Hillard MA, Magyar KL, Ekhlaspour L, Sinha M, et al. Home use of a bihormonal bionic pancreas versus insulin pump therapy in adults with type 1 diabetes: a multicentre randomised crossover trial. Lancet 2017;389(10067):369–80. doi:10.1016/S0140-6736(16)32567-3. [PubMed PMID: 28007348; PMCID: 5358809].

[17] Sherwood JBC, Jafri RZ, El-Khatib F, Maheno M, Hillard M, O'Donovan AJ, et al. Differential effects of the insulin-only and bihormonal configurations of the bionic pancreas on mean glucose and hypoglycemia during the daytime and nighttime; 2018.

[18] Balliro C, Ekhlaspor L, Esmaeili A, El-Kahtib F, Mondesir D, Selagamsetty R, et al. Effect of a lower glucose target on glycemic outcomes with an insulin-only bionic pancreas. Diabetes 2017;66(S1):A280.

[19] Jones GC, Chong ZM, Gilmour J, Matheson C, MacGregor G, Sainsbury CA. Patterns and impact of hypoglycemia, hyperglycemia, and glucose variability on inpatients with insulin-treated cystic fibrosis-related diabetes. Diabetes Therapy 2016;7(3):575–82. Epub 2016/08/24 https://doi.org/10.1007/s13300-016-0194-7. [PubMed PMID: 27550550; PMCID: PMC5014799].

[20] Moran A, Diem P, Klein DJ, Levitt MD, Robertson RP. Pancreatic endocrine function in cystic fibrosis. J Pediatr 1991;118(5):715–23 [Epub 1991/05/01. PubMed PMID: 2019925].