

Editorial

# Where are we in Closing the Loop for Insulin Delivery?

Shah VN<sup>1\*</sup>, Shoskes<sup>2</sup> and Tawfik B<sup>2</sup>

<sup>1</sup>Department of Medicine and Pediatrics, University of Colorado Denver, USA

<sup>2</sup>Department of Medicine University of Colorado Denver, USA

\*Corresponding author: Viral Shah, Department of Medicine and Pediatrics, Barbara Davis Center for Diabetes, University of Colorado, 1775 Aurora Ct, Mail stop A140, Room no 1318, Aurora, Co 80045 USA, Tel: 303-724-8186; Fax: 303-724-6784; Email: viral.shah@ucdenver.edu

Received: July 25, 2014; Accepted: July 28, 2014;

Published: July 30, 2014

## Keywords

Closed-loop insulin delivery; Artificial pancreas; Bionic pancreas; Threshold suspend; Insulin pump; Continuous glucose monitors

## Editorial

The prevalence of type 1 diabetes (T1DM) is rising in certain parts of Europe and the US [1]. In the absence of a cure or prevention of T1DM, insulin is the mainstay for treatment [1,2]. Intensive insulin therapy (IIT) has been shown to reduce micro vascular complications in patients with T1DM and type 2 diabetes (T2DM) [3,4]. However, IIT results in a high incidence of hypoglycemia [5]. Insulin analogs have been shown to reduce hypoglycemia compared to Neutral Protamine Hagedorn (NPH) and regular insulin [6]. With the introduction of insulin pumps and continuous glucose monitors (CGM), the incident rate of hypoglycemia has reduced further [7]. However, despite these insulin analogs and newer technologies, hypoglycemia remains the major obstacle in the management of diabetes, especially T1DM. Keeping blood glucose in the target range without severe hypoglycemia is the major goal for patients, providers, and investigators.

Open-loop insulin delivery using multiple daily injection (MDI) or continuous subcutaneous insulin infusion (CSII) is limited by the introduction of human errors, resulting in hypoglycemia and/or hyperglycemia. Therefore, it is important to connect the CGM and insulin pump by means of various algorithms to control insulin delivery and minimize human error. The system that regulates the delivery of insulin by means of various algorithms to keep blood glucose in normal range is called Closed-loop insulin delivery (CL). It is also known as a bionic pancreas or artificial pancreas. The CL system has attracted many investigators for over three decades, even before commercially available insulin pumps and CGMs, using the cumbersome Kadish artificial pancreas device or the "Biostator" [8,9]. However, the CL system has become a reality with the availability of newer generation smart insulin pumps, CGMs, and refined algorithms. The number of publications on the CL system has increased drastically in the last decade, suggesting a growing interest and efforts of the researchers across the globe. In this Editorial, we

will briefly describe the advances made in the CL system and its future direction.

The CL system has four main components: an insulin pump that delivers insulin, a continuous glucose monitor measures interstitial glucose values every five minutes, algorithms help in modifying insulin delivery based on CGM glucose readings, and glucose meters are required to calibrate the CGM [10].

Since the most feared complication of ITT is nocturnal hypoglycemia, the first logical step in creating an artificial pancreas is to reduce the rate of nocturnal hypoglycemia by means of stopping the delivery of insulin at predetermined low glucose levels [10,11]. This type of CL system is called threshold suspend (TS) in the US and Low Glucose Suspend (LGS) in Europe. The TS (or LGS) system is currently approved by the EMA and FDA, and is the only commercially available component of CL system. LGS stops insulin delivery when the predetermined CGM glucose threshold (between 60-100 mg/dl and can be adjusted by the patient) is reached [10,11]. A number of studies have shown that the use of the TS system reduces the incidence of nocturnal hypoglycemia and time spent in hypoglycemia by 20-40% without worsening glycemic control [11,12]. Another system called the predictive low glucose suspend system (PLGS) uses algorithms to prevent nocturnal hypoglycemia by stop insulin delivery proactively before the hypoglycemic threshold is reached. Many studies have been carried out to assess the feasibility and safety of PLGS and have shown to reduce nocturnal hypoglycemia and time spent in hypoglycemia [13-16]. However, larger clinical trials are required to prove its clinical efficacy, and PLGM has not yet been approved by the FDA. Details on the clinical trials on TS and PLGM are beyond the scope of this review and can be found in reference 9.

Further steps needed to make a near perfect artificial pancreas are 1) hypoglycemia/hyperglycemia minimize 2) hybrid closed-loop 3) fully automated closed-loop and 4) dual hormonal closed-loop [17]. Currently a number of studies have shown that each of the steps mentioned above are feasible in a clinical research setting or supervised out-patient setting [18-22]. The recently published large-scale clinical trial with bi-hormonal CL using glucagon and insulin demonstrated the safety and efficacy of the bi-hormonal CL system in managing T1DM and preventing hypoglycemia [23]. Studies are being carried out to assess the safety of CL use at home by patients. Detailed descriptions of these studies can be found in reference number [10].

Despite the great academic interest and remarkable advances made to date, there are a number of challenges in the way of closing the loop. These challenges are related to the components of the CL system: limitations of currently available sensors, infusion sets, insulin, and algorithms. Despite remarkable improvements in the newer generation of CGMs, they are not accurate at low blood glucose and need frequent calibration using a glucose meter [24]. Infusion sets have a short life span of 48-72 hours. Many patients feel

uncomfortable wearing multiple devices on their skin [25]. Therefore, it is necessary to research increasing the life-span of infusion sets, while combining the CGM with the infusion set. Inter- and intra-individual variability of the currently used rapid acting insulin also makes it difficult for the algorithm to adjust insulin delivery, and the algorithm needs input to account for meals and exercise [25,26]. A number of companies are attempting to make better fast-acting insulin using different technologies, but none have been approved to date. Furthermore, there are challenges with the dual hormone CL system, namely the instability of currently available glucagon and there is no data on the safety of long-term glucagon use [27].

Despite all of the challenges, we hope that the closed-loop system will become a reality and revolutionize the management of diabetes in the near future. A number of ongoing clinical trials hope to bring the artificial pancreas from a clinical research setting to routine day-to-day use by patients. We hope to smell success very soon.

## References

- Atkinson MA, Eisenbarth GS, Michels AW. Type 1 diabetes. See comment in PubMed Commons below *Lancet*. 2014; 383: 69-82.
- Garg SK, Michels AW, Shah VN. Use of non-insulin therapies for type 1 diabetes. See comment in PubMed Commons below *Diabetes Technol Ther*. 2013; 15: 901-908.
- [No authors listed]. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. See comment in PubMed Commons below *N Engl J Med*. 1993; 329: 977-986.
- Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. See comment in PubMed Commons below *N Engl J Med*. 2008; 359: 1577-1589.
- [No authors listed]. Epidemiology of severe hypoglycemia in the diabetes control and complications trial. The DCCT Research Group. See comment in PubMed Commons below *Am J Med*. 1991; 90: 450-459.
- Shah VN, Moser EG, Blau A, Dhingra M, Garg SK. The future of basal insulin. See comment in PubMed Commons below *Diabetes Technol Ther*. 2013; 15: 727-732.
- Yeh HC, Brown TT, Maruthur N, Ranasinghe P, Berger Z, Suh YD, et al. Comparative effectiveness and safety of methods of insulin delivery and glucose monitoring for diabetes mellitus: a systematic review and meta-analysis. See comment in PubMed Commons below *Ann Intern Med*. 2012; 157: 336-347.
- kadish AH. A Servomechanism For Blood Sugar Control. See comment in PubMed Commons below *Biomed Sci Instrum*. 1963; 1: 171-176.
- Young A, Herf S. Biostator Glucose Controller: a building block of the future. See comment in PubMed Commons below *Diabetes Educ*. 1984; 10: 11-12.
- Shah VN, Shoskes A, Twafik B, Garg Sk. Closed-loop system in the management of diabetes: past, present and future. *Diabetes Technol Ther*. 2014, in Press.
- Tauschmann M, Hovorka R. Insulin pump therapy in youth with type 1 diabetes: toward closed-loop systems. See comment in PubMed Commons below *Expert Opin Drug Deliv*. 2014; 11: 943-955.
- Bergenstal RM, Klonoff DC, Garg SK, Bode BW, Meredith M, Slover RH, et al. Threshold-based insulin-pump interruption for reduction of hypoglycemia. See comment in PubMed Commons below *N Engl J Med*. 2013; 369: 224-232.
- Agrawal P, Welsh JB, Kannard B, Askari S, Yang Q, Kaufman FR. Usage and effectiveness of the low glucose suspend feature of the Medtronic Paradigm Veo insulin pump. See comment in PubMed Commons below *J Diabetes Sci Technol*. 2011; 5: 1137-1141.
- Danne T, Tsioli C, Kordonouri O, Blaesig S, Remus K, Roy A, et al. The PILGRIM study: in silico modeling of a predictive low glucose management system and feasibility in youth with type 1 diabetes during exercise. See comment in PubMed Commons below *Diabetes Technol Ther*. 2014; 16: 338-347.
- Buckingham BA, Cameron F, Calhoun P, Maahs DM, Wilson DM, Chase HP, et al. Outpatient safety assessment of an in-home predictive low-glucose suspend system with type 1 diabetes subjects at elevated risk of nocturnal hypoglycemia. See comment in PubMed Commons below *Diabetes Technol Ther*. 2013; 15: 622-627.
- Maahs DM, Calhoun P, Buckingham BA, Chase HP, Hramiak I, Lum J, et al. A randomized trial of a home system to reduce nocturnal hypoglycemia in type 1 diabetes. See comment in PubMed Commons below *Diabetes Care*. 2014; 37: 1885-1891.
- JDRF artificial pancreas project.
- Hovorka R, Allen JM, Eleri D, Chassin LJ, Harris J, Xing D, et al. Manual closed-loop insulin delivery in children and adolescents with type 1 diabetes: a phase 2 randomised crossover trial. See comment in PubMed Commons below *Lancet*. 2010; 375: 743-751.
- Eleri D, Allen JM, Nodale M, Wilinska ME, Mangat JS, Larsen AM, et al. Automated overnight closed-loop glucose control in young children with type 1 diabetes. See comment in PubMed Commons below *Diabetes Technol Ther*. 2011; 13: 419-424.
- Hovorka R, Eleri D, Thabit H, Allen JM, Leelarathna L, El-Khairi R, et al. Overnight closed-loop insulin delivery in young people with type 1 diabetes: a free-living, randomized clinical trial. See comment in PubMed Commons below *Diabetes Care*. 2014; 37: 1204-1211.
- Sherr JL, Cengiz E, Palerm CC, Clark B, Kurtz N, Roy A, et al. Reduced hypoglycemia and increased time in target using closed-loop insulin delivery during nights with or without antecedent afternoon exercise in type 1 diabetes. See comment in PubMed Commons below *Diabetes Care*. 2013; 36: 2909-2914.
- El-Khatib FH, Russell SJ, Magyar KL, Sinha M, McKeon K, Nathan DM, et al. Autonomous and continuous adaptation of a bi-hormonal bionic pancreas in adults and adolescents with type 1 diabetes. *J Clin Endocrinol Metab*. 2014; 99: 1701-1711.
- 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. See comment in PubMed Commons below *N Engl J Med*. 2014; 371: 313-325.
- Lane JE, Shivers JP, Zisser H. Continuous glucose monitors: current status and future developments. See comment in PubMed Commons below *Curr Opin Endocrinol Diabetes Obes*. 2013; 20: 106-111.
- Bequette BW. Challenges and Recent Progress in the Development of a Closed-loop Artificial Pancreas. See comment in PubMed Commons below *Annu Rev Control*. 2012; 36: 255-266.
- Lee JJ, Dassau E, Zisser H, Harvey RA, Jovanovic L, Doyle FJ. In silico evaluation of an artificial pancreas combining exogenous ultrafast-acting technosphere insulin with zone model predictive control. *J Diabetes Sci Technol*. 2013; 7: 215-226.
- Peyser T, Dassau E, Breton M, Skyler JS. The artificial pancreas: current status and future prospects in the management of diabetes. See comment in PubMed Commons below *Ann N Y Acad Sci*. 2014; 1311: 102-123.