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Editorial

Where are we in Closing the Loop for Insulin Delivery?

Shah VN[1]*, Shoskes[2] and Tawfik B[2]

[1]Department of Medicine and Pediatrics, University of Colorado Denver, USA

[2]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

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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 Hegdorn (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 hypoglycemia. 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 helps 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 suspends 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

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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.

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