Automated Insulin Delivery—The Light at the End of the Tunnel

Kamuran Turksoy, PhD[1], Nicole Frantz, BS[1], Laurie Quinn, PhD[2], Magdalena Dumin, MD[3], Jennifer Kilkus, PhD[3], Brooks Hibner, PhD[3], Ali Cinar, PhD[1,3,4], and Elizabeth Littlejohn, MD[3]

Type 1 diabetes mellitus (T1DM) results from autoimmune destruction of pancreatic β cells, resulting in an absolute loss of insulin production, and typically affects youth. Automated insulin delivery (AID) system is a term that has been used over the past 30 years to represent an alternative and incremental improvement in treatment for patients with T1DM. An ideal AID system would use trends from past blood glucose concentrations (BGCs) to normalize them to target, through automatic insulin and glucagon release or by the ingestion of carbohydrate in response to the BGC.

We will briefly review AID technologies that have been developed by different research groups globally, with the objective to familiarize the general pediatric and pediatric endocrinology community about this rapidly developing area of technology that will likely revolutionize therapeutic options for their patients with T1DM. With this goal in mind, this review describes the AID components, reviewing different component brands and algorithms; then presents the human clinical trials that have been conducted under AID control to date; then summarizes the challenges of current AID systems. In conclusion, the future of AID control systems is described.

Automated Insulin Delivery System Components

In general, an AID consists of a sensor that estimates a patient's BGC via measurement of interstitial glucose concentration; a controller with an algorithm to estimate BGC and compute the control command (in single hormone systems, the computed insulin dose or in bihormonal systems, the computed insulin or glucagon dose) transmitted to a pump; and a pump that infuses the computed dose to the patient (**Figure 1**). Several different continuous glucose monitoring (CGM) systems and insulin and/or glucagon pumps with differing control algorithms have been investigated for development of an AID control system. In the subsequent sections, each of the AID components are discussed briefly.

AID	Automated insulin delivery
AP	Artificial pancreas
BGCs	Blood glucose concentrations
CGM	Continuous glucose monitoring
CSII	Continuous subcutaneous insulin infusion
DG4P	Dexcom G4 Platinum
DG5M	Dexcom G5 Mobile
FDA	Food and Drug Administration
FLP	FreeStyle Libre Pro
FN	Freestyle Navigator
FNII	Freestyle Navigator II
GPC	Generalized predictive control
MARD	Mean absolute relative difference
MPC	Model predictive control
PID	Proportional-integral-derivative
SAP	Sensor-augmented pump
SMBG	Self-monitoring of blood glucose
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus

Continuous Glucose Monitors

Currently, there are 2 primary methods used by patients to measure BGCs. These include capillary blood glucose measurements and CGM. Capillary blood glucose testing, or self-monitoring of blood glucose (SMBG), is fraught with variability and concern for accuracy in glucose meters compared with chemistry laboratory testing because SMBG devices may be affected by meter calibration, ambient temperature, size and quality of blood sample, high levels of interfering substances in the blood, hematocrit, humidity, and age of test strips.[2] In addition, patient issues create clinically relevant BGC measurement error (such as sugar-containing substances on fingers that create a falsely high BGC or moist fingers that create falsely low BGC).[3]

CGM is minimally invasive, measuring glucose levels in real-time using subcutaneous sensors to measure glucose levels in the interstitial fluid.[4,5] CGM devices require calibration with SMBG levels at a minimum of twice per day, but there is ongoing research on further minimizing the required calibrations.[6] These devices are most advantageous in that they demonstrate glucose patterns and trends throughout the day rather than just a view of BGC at that instant. This allows patients to better understand their fasting and postprandial glucose trends and the effect of other variables on blood glucose such as physical activity. With SMBG, the patient may fail to recognize hypo- or hyperglycemic episodes if they are asymptomatic and do not happen to check their BGC at that specific time.[4] CGMs enable both the physician and patient to attempt to maintain physiologic glucose levels, adjust the insulin dose,

From the [1]Department of Biomedical Engineering, Illinois Institute of Technology; [2]College of Nursing, University of Illinois at Chicago; [3]Biological Sciences Division, University of Chicago; and [4]Department of Chemical and Biological Engineering, Illinois Institute of Technology, Chicago, IL

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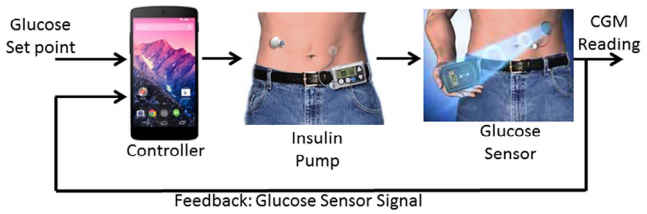

Figure 1. AP.[1]

and (most importantly) prevent dangerous glucose excursions, particularly hypoglycemia. Riveline et al[7] demonstrated that CGM can reduce hemoglobin A1C (a measure of average glucose control over the previous 3 months), as well as time spent in a hypoglycemic state, in both patient-led and physician-driven cohorts. The Juvenile Diabetes Research Foundation CGM randomized controlled trial,[8] the 2006 Guard Control Study,[9] and a recent study by O'Connell et al[10] showed that adults with T1DM who used CGM with SMBG had reduced A1C levels vs SMBG alone and were able to maintain glycemic control for 12 months without an increase in frequency of hypoglycemic excursions.[11] However, there are conflicting data in the pediatric diabetic population, as a meta-analysis by Golicki et al demonstrated no significant difference between CGM vs SMBG in A1C reduction in T1DM youth.[4,11-13] Thus, further research is needed to elucidate CGM effectiveness in the pediatric population. However, there are some disadvantages to the CGM, as the application of the subcutaneous sensor may cause some discomfort, and use of CGMs is limited by high cost.[5]

There are several CGMs on the market today, and these include systems by Medtronic (Northridge, California), Dexcom (San Diego, California), and Abbott (Alameda, California).[4] Several studies have examined CGMs and compared the reference glucose measurements with the corresponding CGM results with a final calculated mean absolute relative difference (MARD), a mathematical calculation that measures the average disparity between the sensor and capillary blood glucose readings obtained simultaneously. The lower the MARD value, the higher CGM performance.[4,11,14] Typically, the MARD is calculated both over the entire sample and in specific ranges such as hypo-, hyper-, and euglycemia. Some studies consider the rate-of-change accuracy of the CGM, additionally, as reliable measurements during rapidly changing BGC are critical.

Each Medtronic CGM communicates directly with specific Medtronic insulin pumps. One Medtronic CGM currently available in the US is the first generation Enlite (**Table I**) sensor, which works with the MiniMed 530G and 630G insulin pumps.[15] The Medtronic Guardian 3 CGM sensor will be released with the MiniMed 670G system in the Spring of 2017.[18] The Dexcom G4 Platinum (DG4P) and its newer version, G5 Mobile (DG5M), are 2 CGMs produced by Dexcom. The DG5M data can be sent directly from the transmitter to a compatible smart device, such as an iPhone, or a standard receiver which if connected to the internet allows for remote monitoring capabilities via a new system called *Share*.[15,19] The DG4P and DG5M systems allows BGC data to be sent from the receiver via Bluetooth to a nearby paired device (eg, iPhone) for remote monitoring capabilities while benefiting from the extended battery life and reliability of the standard Dexcom receiver.[15,19] The DG4P and DG5M come with the Dexcom Studio and Dexcom Clarity software, respectively, that allow the patient to review glucose trends, thus, providing a method for better glycemic control. It is also helpful to providers, as data from the Dexcom mobile app can upload data directly to the clinic's Clarity account if the patient has opted in. The DG5M has been Food and Drug Administration (FDA)-approved to be used in real-time treatment decisions without a confirmatory SMBG value as the Advisory Committee concluded it is sufficiently safe and effective for nonadjunctive use in treatment decisions. The DG5M also has European (European Medicines Evaluation Agency) approval to be used in this manner.[20] Abbott developed the Freestyle Navigator (FN), the Freestyle Navigator II (FNII), and the FreeStyle Libre Pro (FLP).[21] The FNII sensor measures glucose every 1 minute and also provides glucose averages over 10 minutes.[4] The FNII has a built-in blood glucose meter that allows for easier calibration. The FLP is factory calibrated and does not require calibration via blood glucose meter. It is unique in that it does not continuously send the glucose values to a receiver but rather stores the data in the sensor that can be retrieved with its scanner.[16] The FLP is available for clinic use only. Patients can wear it for up to 14 days at which time the data is retrieved. Additional technical information and a comparison of commercially available CGMs can be found in **Table I**.

When Damiano et al[17] compared them directly, the DG4P and FN had a significantly lower MARD and a significantly lower rate of very large errors than the first generation Enlite. This study did not find a significant difference between these metrics for the DG4P and FN sensors. These reported CGMs

Table I. Comparison of CGM sensors[4,15-17]

CGMs	MARDs	Calibration frequency	Water-resistance	Sensor lifespan	Receiver operating range
E1	13.6%	12 h	8 ft for 30 min	6 d	Insulin pump is receiver
G3	10.3%	12 h	8 ft for 30 min	7 d	Insulin pump is receiver
DG4P	13%	12 h	8 ft for 24 h	7 d	20 ft
DG5M	9%	12 h	8 ft for 24 h	7 d	6 m
FNII	12.3%	12 h	1 m for 45 min	5 d	30 ms
FLP	11.4%	Factory calibrated	1 m for 30 min	14 d	1.5 in

E1, first generation Enlite; *G3*, Guardian 3.