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REVIEW ARTICLE

Current Status and Emerging Options for Automated Insulin Delivery Systems

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Abstract

Combining technologies including rapid insulin analogs, insulin pumps, continuous glucose monitors, and control algorithms has allowed for the creation of automated insulin delivery (AID) systems. These systems have proven to be the most effective technology for optimizing metabolic control and could hold the key to broadly achieving goal-level glycemic control for people with type 1 diabetes. The use of AID has exploded in the past several years with several options available in the United States and even more in Europe. In this article, we review the largest studies involving these AID systems, and then examine future directions for AID with an emphasis on usability.

Keywords: Type 1 diabetes, Hybrid closed loop, Automated insulin delivery, Artificial pancreas.

Introduction

THE LANDMARK DIABETES Control and Complications Trial (DCCT) established the benefits of intensive insulin therapy, including basal-bolus insulin administration and tight glycemic control.¹ Despite the well-established findings from this study, real-world replication of the intensive glycemic control from the DCCT intervention arm has been allusive.^{2,3} Combining technologies including rapid insulin analogs, insulin pumps, continuous glucose monitors (CGMs), and control algorithms has allowed for the creation of automated insulin delivery (AID) systems. AID systems can be considered any design where insulin delivery is increased and decreased automatically based on an algorithm, consisting of both hybrid closed loop (HCL), which requires user interaction for meal and correction boluses, and fully closed loop, which may not require user interaction.

AID systems have proven to be the most effective technology for optimizing metabolic control⁴⁻⁹ and could hold the key to broadly achieving goal-level glycemic control for

people with type 1 diabetes (T1D). In this review article, we will provide an overview of the major pivotal and real-world clinical trials for AID systems around the world, and then provide expert perspectives on areas of AID development to further reduce the burden and improve benefit of diabetes technologies.

Pivotal Trial Review

Medtronic 670G, 770, and 780G trials

Commercial HCL technology first received regulatory approval on September 28, 2016, when the U.S. Food and Drug Administration (FDA) approved the Medtronic MiniMed 670G for people 14 years of age and older with T1D.¹⁰ FDA approval of a medical device certifies that a device is safe and effective and allows for legal marketing of the device within the United States. The Medtronic MiniMed 670G is a HCL system utilizing the Medtronic 600 series CSII pump, the Guardian Sensor 3 CGM, and an algorithm to automate basal insulin delivery to reduce both hypoglycemia

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and hyperglycemia.^{11–15} The algorithm has been described as a proportional integral derivative control approach, although additions of an insulin feedback term as well as other constraints on the algorithm make this more of a hybrid control approach.^{14,15}

Approval for this system was based on a single-arm study comparing home use of the 670G system over 3 months with 2 weeks of run-in (baseline) data among 124 participants 14–75 years old (Table 1).^{16,17} The major safety outcomes showed no episode of severe hypoglycemia (SH) or diabetic ketoacidosis (DKA) over 12,389 days of system use.¹⁶

The major glycemic endpoints demonstrated reduction in hemoglobin A1c (HbA1c) from 7.7% ± 0.8% to 7.1% ± 0.6% (*P* < 0.001) among adolescents and from 7.3% ± 0.9% to 6.8% ± 0.6% (*P* < 0.001) among adults with time in range (TIR) 70–180 mg/dL increased from 60.4% ± 10.9% to 67.2% ± 8.2% (*P* < 0.001) and 68.8% ± 11.9% to 73.8% ± 8.4% (*P* < 0.001) in adolescents and adults, respectively.¹⁷ Both adolescents and adults also saw a decrease in level 1 hypoglycemia (CGM time <70 mg/dL) as well as variability as expressed by standard deviation or coefficient of variation (CV).¹⁷

The 670G system then received FDA approval in the 7–13-year-old age group on June 21, 2018, based on a second single-arm study, also comparing 3 months of home use of the system to 2 weeks of run-in data (Table 1). The 7–13-year-old study also met safety endpoints with no episode of SH or DKA during the study phase. Glycemic control endpoints demonstrated a reduction in HbA1c from 7.9% ± 0.8% to 7.5% ± 0.6% (*P* < 0.001) with improvement in TIR from 56.2% ± 11.4% to 65.0% ± 7.7% (*P* < 0.001).¹⁸ This population also saw a decrease in level 1 hypoglycemia as well as variability as expressed by standard deviation or CV.¹⁸

On August 31, 2020, the Medtronic MiniMed 770G received FDA approval with expanded indications into the 2–6-year-old age group. The 770G system utilizes the same control algorithm and CGM as the 670G system, but updates the pump to the 700 series model, which has improved user interfaces as well as Bluetooth connectivity between the pump and a smartphone. The 2–6-year-old data again demonstrated no episode of SH or DKA, while showing improved TIR from 55.7% ± 13.4% to 63.8% ± 9.4% (*P* < 0.001) with HbA1c reduction from 8.0% ± 0.9% to 7.5% ± 0.6% (*P* < 0.001).¹⁹

The Medtronic MiniMed 780G system utilizes the 700 series model pump along with Medtronic’s Advanced Hybrid Closed Loop (AHCL) algorithm and either the Guardian Sensor 3 or Guardian Sensor 4 CGM. The AHCL algorithm utilizes more aggressive correction boluses for hyperglycemia and more accommodative parameters to remain in automated mode.²⁰ Studies on the 780G system have compared it against either predictive low glucose minimization (PLGM) or the 670G systems. When compared against PLGM, the 780G demonstrated an improved TIR of +11.8% ± 7.4% (*P* < 0.001) in children 7–13 years old, +14.4% ± 8.4% (*P* < 0.001) in adolescents 14–21 years old, and +11.9% ± 9.5% (*P* < 0.001) in adults 22–80 years old with overall TIR of 80.4% ± 8.1%.²¹

When compared with the 670G system, the ACHL system demonstrated an improved TIR of 67% versus 63% (*P* < 0.0001) with improved percent time in auto mode of 86% versus 75% (*P* < 0.0001).²² On June 11, 2020, the

TABLE 1. SELECT METRICS FROM DEVICE PIVOTAL TRIALS

Device	Adults or adults/adolescents										Children						
	TIR 70–180 mg/dL (%)	Mean SG (mg/dL)	HbA1c (%)	TAR >250 mg/dL (%)	TAR >180 mg/dL (%)	TBR <70 mg/dL (%)	TBR <54 mg/dL (%)	%CV	Source	TIR 70–180 mg/dL (%)	Mean SG (mg/dL)	HbA1c (%)	TAR >250 mg/dL (%)	TAR >180 mg/dL (%)	TBR <70 mg/dL (%)	TBR <54 mg/dL (%)	%CV
Medtronic 670G	68.8/67.2	148.3/158.5	6.8/7.1	1.3/2.8 ^a	22.8/30.0	3.4/2.8	0.6/0.5 ^a	30.3/32.2	Garg—DTT, 2017	65.0	162	7.5	10.3	32.0	3.0	0.8	33.7
Medtronic 780G	75.1/72.7	147/150	7.0/7.1	4.3/5.6	22.6/24.9	2.3/2.4	0.5/0.6	33.7/35.7	Carlson—DTT, 2021	Not yet reported	Not yet reported	Not yet reported	Not yet reported	Not yet reported	Not yet reported	Not yet reported	Not yet reported
Tandem Control IQ	71	156	7.06	5.2	27	1.58	0.29	34	Brown—NEJM, 2019	67	162	7.0	7.8	31	1.6	0.2	38
Insulet OP5	73.9	154	6.78	5.8	24.7	1.32	0.23	31.7	Brown—DC, 2021	68.0	160	6.99	9.6	30.2	1.78	0.32	37.0
CamAPS FX	65	160.2	7.4	3.5 ^b	32	2.6	0.3 ^b	40	Tauschmann—Lancet, 2018	Included in the adult/adolescent data	Included in the adult/adolescent data	Included in the adult/adolescent data	Included in the adult/adolescent data	Included in the adult/adolescent data	Included in the adult/adolescent data	Included in the adult/adolescent data	Included in the adult/adolescent data
Diabeloop	68.5	156.6	7.3	7.4	29.5	2.0	0.2	31.0	Berhamou—Lancet Digital Health, 2019	Not yet reported	Not yet reported	Not yet reported	Not yet reported	Not yet reported	Not yet reported	Not yet reported	Not yet reported

^aThe Garg 670G trial reported TBR <50 mg/dL instead of <54 mg/dL and TAR >300 mg/dL instead of >250 mg/dL.

^bThe Tauschmann CamAPS FX trial reported TBR <2.8 mM instead of <3.0 mM and TAR >16.7 mM instead of 13.9 mM. CV, coefficient of variation; HbA1c, hemoglobin A1c; SG, sensor glucose; TAR, time above range; TBR, time below range; TIR, time in range.

Medtronic 780G received a CE mark for us in people 7–80 years old. A CE mark means that a product meets the General Safety and Performance Requirements of all relevant European Medical Device Regulations and allows for legal marketing of the Device within the European Union. The 780G system is being paired with the factory-calibrated Guardian Sensor 4 CGM. In a single-arm U.S. study, the 780G system maintained time in closed loop of $94.9\% \pm 5.4\%$ with TIR of $74.5\% \pm 6.9\%$ and an HbA1c of $7.0\% \pm 0.5\%$.²³

Tandem Control-IQ

The Tandem Control-IQ (CIQ) HCL system utilizes the Tandem t:slim X2 insulin pump, Dexcom G6 CGM, and the CIQ HCL algorithm. The CIQ algorithm is a model predictive control (MPC) algorithm developed by the University of Virginia, which has been extensively described during development.^{24–26} CIQ utilizes user-programmed basal rates and correction sensitivity settings to automate hypoglycemia and hyperglycemia reduction through both basal modulation and periodic auto correction boluses.

The CIQ system was FDA authorized on December 13, 2019, for people 14 years of age and older. This initial approval was based on a randomized controlled trial of people 14 to 71 years of age, comparing CIQ users against people using sensor-augmented pump (SAP) therapy (Table 1).²⁷ This trial demonstrated improved TIR in the CIQ group from $61\% \pm 17\%$ to $71\% \pm 12\%$ while the SAP group's TIR remained unchanged at $59\% \pm 14\%$ (mean adjusted difference, 11%, $P < 0.001$).²⁷ Hierarchical analysis of secondary outcomes also demonstrated significant reductions in time >180 mg/dL, mean sensor glucose level, HbA1c, and level 1 hypoglycemia.

The CIQ system was authorized for people 6–13 years of age on June 17, 2020. This approval was based on a second randomized controlled trial of people 6–13 years of age, again comparing CIQ against SAP therapy (Table 1).²⁸ This pediatric study demonstrated improved TIR from $53\% \pm 17\%$ to $67\% \pm 10\%$ in the CIQ group compared with $51\% \pm 16\%$ to $55\% \pm 13\%$ in the SAP group (mean adjusted difference, 11%; $P < 0.001$).²⁸ Hierarchical analysis of secondary outcomes demonstrated significant reductions in time >180 mg/dL and mean sensor glucose, but not HbA1c. Level 1 hypoglycemia remained in the 1.0%–1.8% range at both time points for both groups.

A pilot study of the CIQ system with modified parameters in children 2–5 years of age investigated the use of the system in a supervised hotel/house setting followed by remote-monitored outpatient use.²⁹ The study tested the CIQ Pro algorithm, which is a slightly modified version of CIQ allowing for lower total daily dose settings than CIQ. This single-arm pilot demonstrated improved TIR in this age group from $63.7\% \pm 15.1\%$ at baseline to $71.3\% \pm 12.5\%$ with system use ($P = 0.016$).²⁹ The modified CIQ system is now being tested in an NIH-sponsored U01 trial for commercial approval down to age 2 years.

Insulet Omnipod 5

The Insulet Omnipod 5 (OP5) HCL system utilizes an on-body Bluetooth-enabled patch pump (pod) containing an on-board MPC algorithm communicating with a Dexcom G6 CGM and smartphone app.³⁰ At the time of this submission,

the OP5 HCL system is pending FDA approval. The total daily insulin dose is initialized from the system's programmed basal rate and then updates with every pod change, about every 3 days. The basal modulation is then determined by the system based on the total daily dose, while corrections and meal boluses are based on programmed carbohydrate ratios, correction factors, and targets. The basal modulation is also impacted by the system target, which can be set at 110, 120, 130, 140, or 150 mg/dL with up to eight targets per day.

The OP5 HCL system is pending FDA approval for use in the United States in ages 6+ years. The single-arm pivotal trial of the OP5 system compared 2-week standard therapy glucose control against 3 months of HCL control in 112 children (6–13.9 years old) and 129 adults/adolescents (14–70 years old) (Table 1). The trial demonstrated improved HbA1c in children (7.67 ± 0.95 vs. 6.99 ± 0.63 ; $P < 0.0001$) and adults/adolescents (7.16 ± 0.86 vs. 6.78 ± 0.68 ; $P < 0.0001$) in standard therapy versus HCL therapy.³¹ TIR in children (52.5 ± 15.6 vs. 68.0 ± 8.1 ; $P < 0.0001$) and adolescents/adults (64.7 ± 16.6 vs. 73.9 ± 11.0 ; $P < 0.0001$) was also significantly improved.³¹

The OP5 system has also completed pivotal testing in children 2–5.9 years old. The study in this age group uses the exact same build and algorithm as was used in the 6+-year-old age group study above. The 3-month single-arm trial also compared 2-week standard therapy glucose control against 3 months of HCL control, in this case among 80 children 2 to 5.9 years old.³² The trial demonstrated improved HbA1c (7.4 ± 1.0 vs. 6.9 ± 0.7) and TIR (57.2 ± 15.3 vs. 68.1 ± 9.0) in the standard therapy versus HCL phases.³²

Data on the first 6 months of OP5 use within the trial's extension phase have been presented. It should be noted that, unlike the previous real-world data discussed, these data still represent clinical trial participants selected for trial participation and receiving the device and supplies free from the manufacturer. These extension data demonstrated sustained HbA1c and TIR improvement between 3 and 6 months of system use when compared to the 3-month pivotal trial results.³³

CamAPS FX

CamAPS FX is an MPC algorithm developed at the University of Cambridge. Publications regarding the algorithm date back to 2010 when CGM values from a Medtronic Guardian Real-Time or FreeStyle Navigator were manually entered onto a computer and the system output a basal rate change that was manually entered into a Deltec Cozmo insulin pump by a research nurse.³⁴ This article and those that followed^{35–39} provided ample clinical evidence for increased TIR with reduced hypoglycemia⁴⁰ in those living with T1D, who used the algorithm.

The work culminated in a 2018 Lancet publication describing an international multicenter, open-label, randomized trial among 86 individuals with T1D age 6 years and older (Table 1).⁴¹ The authors show 12-week use of the hybrid closed-loop insulin delivery system compared with sensor-augmented pump therapy was associated with an improvement in TIR (65% for closed-loop and 54% for control group, $P < 0.0001$), reduction in HbA1c (8.3% \rightarrow 7.4% for closed loop and 8.2% \rightarrow 7.7% for control, $P < 0.0001$), and no SH. CamAPS FX received CE mark in March 2020

and is the only system labeled for pregnancy and children down to 1 year of age. The algorithm runs on Android phone and currently works with the Dexcom G6 and DANA Diabcare RS pump.

Of note, during the Day and Night Closed loop in Young People With T1D (DAN05, NCT02925299) trial, the system used varied by country. In the United States, the FlorenceM platform consisted of a Medtronic 640G, Guardian3 sensor, and Android phone with case that allowed wireless communication to the pump. In United Kingdom, the FlorenceX platform consisted of a DANA Diabcare R pump, Dexcom G6 sensor, and Android phone that communicated with devices through native Bluetooth. The FlorenceM system had significantly more connectivity and usability issues, including a sensor that required calibrations. The specific system configurations were associated with efficacy, highlighting the importance of the system as a whole and not simply the algorithm.

Diabeloop

In 2017, a multicenter French open-label randomized controlled 12-week crossover trial of the Diabeloop Generation 1 (DBLG1) system was conducted among 63 individuals with T1D (Table 1).⁴² The Diabeloop algorithm was implemented in an Android app with a Cellnovo insulin patch pump and Dexcom G5 CGM. After 12 weeks of therapy, TIR in the DBLG1 group was 68.5% ± 9.4% versus 59.4% ± 10.2% in the sensor-augmented pump group. Five SH events occurred in the DBLG1 group and three in the SAP group.

Diabeloop received the CE mark in November 2018. It is currently compatible with Roche's Accu-Chek Insight, ViCentra's Kaleido, SOOIL's Dana-I, and Cellnovo insulin pumps. It supports Dexcom CGMs and has a diabetes data management platform called YourLoops.

Real World Data

Medtronic 670G, 770, and 780G

Numerous studies by groups from all over the world have investigated the performance of the Medtronic 670G system among clinical populations outside the selection bias and additional supports of industry- or government-sponsored clinical trials. Data from selected real-world studies will be presented here. In 2019, Lal published 1 year of observational data among 79 people, 9–61 years of age, using the 670G system at Stanford University.⁴³ This study demonstrated at least 28% discontinuation of Auto Mode by 3 months and at least 33%–35% discontinuation between 6, 9, and 12 months. Reasons for system discontinuation included sensor issues, problems obtaining supplies, and hypoglycemia fear.⁴³ This study also demonstrated a significant correlation between increased time in Auto Mode and decreased HbA1c.

A series of studies conducted by Berget, Messer, and Akturk at the Barbra Davis Center examined the 670G in both pediatric and adult populations. Berget examined the use of the 670G among 92 children over 6 months and demonstrated significant decline in Auto Mode use from 65.5% ± 3.0% at 1 month to 51.2% ± 3.4% ($P=0.001$) at 6 months.⁴⁴ Over this period, HbA1c decreased from 8.7% ± 0.2% at baseline to 8.4% ± 0.2% ($P=0.2$) at 6 months. During this time, 30% of participants discontinued Auto Mode use. Messer examined

predictors and perceptions among the discontinuers and found that baseline HbA1c predicted discontinuation with each 1% increase in HbA1c being associated with 2.7-fold increased odds of Auto Mode discontinuation.⁴⁵

This analysis also showed that technological difficulties, too much work, and frequent alarms were the major drivers of Auto Mode discontinuation. Akturk examined 6 months of 670G use among 127 adults using the 670G system.⁴⁶ This analysis demonstrated an HbA1c decrease of 0.4% by 3 months, which was maintained over 6 months (7.6% ± 0.07% vs. 7.2% ± 0.08%; $P<0.001$).⁴⁶ The analysis also showed that higher time in Auto Mode was associated with improved glucose outcomes. Berget also conducted a combined analysis of the original pediatric and adult cohorts over a 12-month follow-up period.⁴⁷ This analysis of 276 670G users demonstrated that overall, youth struggled with maintaining Auto Mode use more than adults did. It also demonstrated that older age, higher CGM use, and four or more blood glucose tests per day were associated with attaining higher Auto Mode use.

Medtronic CareLink data of the first 3141 users of the 670G system were reported by Stone.⁴⁸ This real-world analysis demonstrated overall Auto Mode use of 87.2% with TIR of 72.4% and mean sensor glucose of 151 ± 14 mg/dL.⁴⁸ The authors note that this compares favorably with the pivotal trial data on the 670G system.

The 780G received CE mark in June 2020. Medtronic has also reported real-world data among 780G AHCL users in Europe based on CareLink data.⁴⁹ This analysis of 4120 individuals observed for 54 ± 32 days showed that they spent 94.1% ± 11.4% time in Auto Mode. The 780G users had a mean TIR of 76.2% ± 9.1% with a glucose management index (GMI) of 6.8% ± 0.3%.⁴⁹ In addition, 77.3% of users achieved a TIR at or above the American Diabetes Association goal of 70% and 79.0% had a GMI of <7.0%.

Tandem CIQ

Breton and Kovatchev have published 12 months of real-world use of the Tandem CIQ system based on data obtained from Tandem's t:connect web application.⁵⁰ This analysis describes glycemic data from 9451 CIQ users with either type 1 or type 2 diabetes. Overall, the percent time in automated mode was 94.2% for the entire 12-month duration with no significant changes over time.⁵⁰ TIR increased significantly from a baseline of 63.6% to 73.6% for the 12 months of use with no significant changes over time. Subanalysis of these data looked at glycemic improvements in users with higher baseline GMI values.⁵¹ Among 242 users with baseline GMI ≥9%, GMI declined from 9.5% to 8.1% ($P<0.001$) and TIR increased from 19.6% to 46.7% ($P<0.001$). Among 36 users with baseline GMI ≥10%, GMI declined from 10.5% to 8.6% ($P<0.001$) and TIR improved from 10.5% to 38.6% ($P<0.001$).⁵¹

Diabeloop

After receiving the CE mark, the Diabeloop consortium published the 6-month experience of 25 select users who started the system.⁵² Participant age ranged from 25 to 72 years. At baseline, mean HbA1c was 7.9% ± 0.9%, which decreased to 7.1% following 6 months of Diabeloop use ($P<0.001$). TIR was 53% ± 16.4% at baseline, which

increased to 69.7% following the intervention ($P < 0.001$). One patient stopped using the system after 2 months. There were no reported serious adverse events.

Open-source AID

Open-source AID is fully transparent software developed by a community of people with diabetes and their loved ones. One of the first open-source diabetes software packages was Nightscout, a real-time CGM data management platform, enabling remote monitoring with initial release in 2014. Shortly thereafter, in 2015, OpenAPS was released—it utilized Nightscout as a CGM data source and a linux-based computer and wireless radio to alter insulin delivery on Medtronic pumps that could receive arbitrary remote commands. Another system, Loop, which ran on iOS (described in detail in the next section), followed in 2016. The OpenAPS algorithm was eventually implemented as an app on Android, dubbed AndroidAPS, and iOS as FreeAPS X. These open-source AID systems are compatible with a variety of insulin pumps and CGMs.

Several efforts have been undertaken to understand the real-world safety and efficacy of these systems in aggregate. One such effort published in 2019 was a self-report of clinical outcomes among 209 caregivers of children with diabetes from 21 countries.⁵³ Caretakers reported decrease in HbA1c from $6.9\% \pm 0.9\%$ to $6.3\% \pm 0.7\%$ ($P < 0.001$) and increase in TIR from $64.2\% \pm 15.9\%$ to $80.7\% \pm 9.3\%$ using open-source AID for a median duration of 7.5 months.

A 2021 study among 897 participants (80.5% adults and 19.5% children) with diabetes from 35 countries elucidated motivations for the use of open-source AID and self-reports of glycemia.⁵⁴ Reasons for using these systems were improving glycemic outcomes, sleep quality, life expectancy, and reducing complications and diabetes workload. In addition, many did not have access to a commercial AID system or were not achieving goals on current available therapies. HbA1c improved from $7.1\% \pm 1.1\%$ to $6.2\% \pm 0.6\%$ ($P < 0.001$) and TIR increased from $63.0\% \pm 16.2\%$ to $80.3\% \pm 9.4\%$ ($P < 0.001$).

Loop

The open-source automated insulin dosing app, Loop, was developed in 2016 and runs on iOS and works with Medtronic/Dexcom CGMs, Medtronic pumps that allowed for arbitrary remote commands over 916 MHz, and the OmniPod Eros over 433 MHz. The Phone communicates through Bluetooth to a sub-GHz radio bridge that conveys commands to the pump. The software gained significant popularity, and in 2019, a real-world prospective observational study⁵⁵ was undertaken to evaluate outcomes in 558 adults and children (age 1–71 years), who started using the system and provided data for 6 months.

Mean TIR increased from $67\% \pm 16\%$ at baseline to $73\% \pm 13\%$ during the 6 months ($P < 0.001$). Mean HbA1c decreased from $6.8\% \pm 1.0\%$ at baseline to $6.5\% \pm 0.8\%$ after the 6 months ($P < 0.001$). SH was 181 per 100 person-years during the 3 months before study and was reduced, by an order of magnitude, to 18.7 per 100 person-years. The Jaeb Center for Health Research, responsible for running a multitude of commercial diabetes technology trials, concluded the system was safe and effective to initiate with community-developed resources.

Future Perspectives on Usability

Extended wear infusion sets

All current AID systems approximate active insulin remaining in the body, to prevent insulin overdosing or predict future glucose. This estimate presumes that all delivered insulin makes it into the subcutaneous space. However, it is known that the infusion set can become occluded or kinked and local inflammation and infection around the site can result in insufficient insulin delivery, high glucose levels, ketoacidosis, and death.^{56,57}

Previously insulin infusion sets were approved for only 2–3 days. The Medtronic extended wear infusion set received a CE mark and FDA approval for 7-day wear in July 2021, although the trial data have not been published at the time of submission of this article. Trials for other extended wear sets are underway by ConvaTec⁵⁸ and Capillary Biomedical. Extended wear infusion sets directly improve the usability of insulin pumps by reducing the time required to maintain the device, the number of required insertions, and reducing the body surface area required for use. When discussing different products, it is important to understand that there has not been a consistent approach to defining infusion set failure in extended wear studies, making comparisons between different products challenging.

Combined CGM and insulin infusion set

Data from the T1D Exchange in 2016 reported that out of 1006 adults wearing CGM, 27% discontinued CGM use after 1 year and of those, 33% explained that they were using a pump and did not want to have devices on two sites of their body.⁵⁹ With the advent of extended-wear infusion sets, the possibility now exists for an all-in-one infusion set and CGM single-port device to alleviate the burden of wearing multiple devices. Current infusion sets are approved for 2–3 days of wear,^{60,61} while sensors are approved for 7–14 days of wear with greater accuracy after the first day.⁶² Creating a combined sensor and insulin infusion set requires an extended-wear infusion set.

Previous attempts to make a single combination device were not practical due to limited infusion set longevity.^{63–66} Tschaike reported combining off-the-shelf CGM and infusion sets by running the sensor wire through the cannula,⁶⁵ such that the sensor tip was 6 mm from the cannula opening. The sensor glucose obtained from the combination device did not differ significantly from a separately worn CGM.⁶⁶ Human studies are now underway for a commercial combination device, the Medtronic DUO Extended Set (NCT04823312). A single-port device is likely to improve device wearability and may encourage more people to pursue AID.

Noninvasive CGM

Multiple reviews of noninvasive CGM have been previously published and the details of these systems are beyond the scope of this review.⁶⁷ Transdermal methods of sensing include reverse iontophoresis (utilized in the GlucoWatch), sonophoresis, impedance spectroscopy, and interstitial fluid-filled blister technique. Light, sound, and thermal sensing are increasingly being considered for noninvasive CGM: contact lens-based ocular spectroscopy, electromagnetic sensing, fluorescence, infrared spectroscopy, near-infrared spectroscopy,

mid-infrared spectroscopy, far-infrared spectroscopy, kromoscopy, metabolic heat conformational technique, millimeter/microwave sensing, occlusion spectroscopy, optical coherence tomography, photoacoustic spectroscopy, polarimetry, Raman spectroscopy, scattering, temperature-regulated localized reflectance, terahertz time-domain spectroscopy, thermal emission spectroscopy, and ultrasound.

These technologies may encourage more individuals to use CGM and perhaps increase the uptake of AID. Popular press has suggested that Apple and Samsung may be attempting to integrate optical sensors for CGM into their smartwatches. Benefits of this integration include widespread adoption of smartwatches and the elimination of disposable costs allowing for equitable access to CGM technology. In addition, if some of the incoming signal comes from the vascular compartment, one could decrease the latency that results from interstitial glucose sensing. These expectations must also be tempered by the difficult regulatory pathway that exists for iCGM, especially if these technologies require machine learning.

New insulins

When discussing development of improved HCL systems and progress toward completely automated systems, the pharmacokinetic and pharmacodynamic properties of current commercial insulins is frequently described as a major limiter of progress. There has long been hope that newer “ultra-rapid” acting insulins, such as faster aspart (Fiasp) and ultra-rapid lispro (Lyumjev), will play a role in reducing this barrier.^{68,69} In multiple daily injection studies, these insulins have demonstrated the ability to reduce postprandial glucose values when compared to their conventional rapid acting insulin counterparts.^{68,69}

Unfortunately, studies of ultra-rapid acting insulins in HCL systems have generally demonstrated modest results. A double-blind randomized crossover trial of rapid-acting aspart against ultra-rapid acting faster aspart looked at TIR during 2 weeks of Medtronic 670G use.⁷⁰ This study demonstrated clinically similar TIR values of $75.3\% \pm 9.5\%$ with aspart and $78.4\% \pm 9.3\%$ with faster aspart.⁷⁰ A separate study analyzed lispro against ultra-rapid lispro in double-blind randomized crossover trial for 4 weeks using the 670G system.⁷¹ This study also demonstrated clinically similar TIR values of 77.8% with lispro and 77.0% with ultra-rapid lispro.⁷¹ Additional developmental studies are ongoing to look at further improvements with modified algorithm parameters, including during meal announcement and with fully autonomous designs.

Machine learning

In the modern era, machine learning is a technique that is thrown at a multitude of problems. Diabetes is no exception and there have been hundreds of articles published on the topic.⁷² Indeed, several neural network-based software packages have regulatory approval for the detection of diabetes-related retinopathy.⁷³

Crucially, predicting glucose dynamics in every circumstance has eluded even the most complex systems. Having more accurate information will certainly generate more robust models, but these systems may still have difficulty predicting sudden acute changes without additional informa-

tion. Future AID systems utilizing machine learning strategies may require overrides for periods of time that deviate significantly from the standard model established for an individual living with diabetes. These may include situations such as illness, intense activity at unpredictable times (e.g., diabetes camp or marathon), and when moving through time zones.

Multihormone systems

Several groups have targeted their efforts on utilizing hormones, other than insulin, in glucose control systems. These systems may offer safety for exercise and potential for fully AID without information from the user. However, usability is an especially important concern if these other hormones are not co-formulated with insulin.

The iLet bionic pancreas (Beta Bionics, Inc.) developed out of Massachusetts is a closed-loop system intended for use with insulin and glucagon. An open-label, randomized crossover trial of the system for 7 days with and without glucagon was conducted among 10 participants, age 21–74 years, with T1D.⁷⁴ TIR was $72\% \pm 8\%$ in the insulin-only system and $79\% \pm 9\%$ in the bihormonal implementation. The bihormonal system does require wearing an extra infusion set for dasiglucagon administration, but the system only requires body weight for initialization and meal announcements are described as small, medium, or large without the need for a specific carbohydrate count. There is a tradeoff between wearing another infusion set against increased TIR and decreased work of meal announcement.

Another glucagon and insulin system was tested at Oregon Health & Science University. This was a single-center, randomized, open-label trial comparing an insulin-only predictive low-glucose suspend system with an insulin and glucagon system among 23 adults with T1D.⁷⁵ The primary outcome was percent time <70 mg/dL from start of in-clinic aerobic exercise to 4 h afterward. Median time <70 mg/dL was 0.0 (0.0 and 4.2)% for the dual hormone system and 8.3 (0.0 and 12.5)% in insulin-only system ($P=0.025$).

This reduction in hypoglycemia was balanced with an increase in percent time >180 mg/dL, 20.8% in the dual hormone system versus 6.3% in the insulin-only system ($P=0.038$). Overall, TIR was significantly higher ($P=0.044$) for dual hormone system (71.0%) versus insulin-only system (63.4%). Again, there is a tradeoff between wearing more devices and having more freedom to exercise safely and without the need for consumption of extra carbohydrates.

An additional closed-loop design reported to be under development is based on system designed at McGill University in collaboration with Eli Lilly for commercialization.⁷⁶ While much of the commercial design is likely not finalized, the control approaches being developed by the Haidar group are quite notable. This group has published numerous studies on dual hormone systems involving rapid and ultra-rapid acting insulins along with pramlintide.^{77–79} Pilot studies of this system have demonstrated the ability to safely deliver ultra-rapid acting insulin and pramlintide using only meal announcement and even in a fully closed-loop manner.⁷⁷ TIR values reported with this system have been in the 74%–84% range during limited pilot testing.^{77,78} Co-formulation of insulin and amylin would increase the usability of this system tremendously, but will require a fixed drug ratio.

Novel sensing of additional analytes

As new sensing technologies arise, the ability to detect compounds beyond glucose becomes possible. Many newer forms of sensing utilize machine learning, in particular neural networks, to translate incoming sensor signal to a gold standard measurement (e.g., glucose). If these techniques receive regulatory approval, alternate sensing modalities may be able to detect additional analytes. A 2020 review by Wolkowicz and colleagues covers some of the more important measurements for AID systems.⁸⁰ Insulin sensing, while technically challenging, can provide a true measure of insulin-on-board and detect infusion set failure if measured levels are below predicted.

Ketone sensing is less technically challenging and may be useful for detecting absolute insulin deficiency and DKA or evaluating fat burning in those attempting to lose weight. Lactate sensing may be useful in detecting prolonged activity/exercise and provide an early indicator for severe illness. Quantifying cortisol, epinephrine/norepinephrine, glucagon, and growth hormone concentrations could be correlated with the current degree of insulin resistance and increase or decrease the aggressiveness of an AID controller to match current conditions. Finally, alcohol sensing may be useful to predict changes in hepatic gluconeogenesis correlated with basal rates and give early alerts for impaired self-awareness.

Cloud tuning

As diabetes technology reaches more people living with diabetes, uploading the data on these devices has become crucial for providing clinical care. From a usability perspective, requiring users to actively perform these uploads can be cumbersome. Nightscout, for example, has allowed passive real-time data logging since its inception. Among commercial and emerging AID systems, each has a proprietary data platform either through the company (e.g., Medtronic CareLink, Tandem t:connect, and Dexcom Clarity) or an exclusive partnership (e.g., Insulet and Glooko). There also exist third party platforms, which provide support for a wide ranging and rapidly changing list of devices. Such platforms include Glooko (supports Medtronic 670G, and Tandem t:slim X2, and will support Insulet OP5) and Tidepool (supports Medtronic 670G, Tandem t:slim X2, and current Insulet Omnipod products).

Tuning of AID system settings (e.g., targets, basal rate, carbohydrate-to-insulin ratio, insulin sensitivity factors, and overrides) continue to be an area of both user and provider focus. With the current and emerging system designs, the settings that can be tuned vary from device to device. This results in complexity and confusion among many providers who may be unaware that settings for a given system may not affect the behavior of the automation uniformly. Laurel Messer, RN, PhD, with the Barbara Davis Center has developed a free tool kit for users and providers to understand which settings are tunable based on the published CARES framework available at <https://www.bdcpantherdiabetes.org/>.⁸¹

A potential solution to the challenges of AID device tuning is the use of cloud-based tuning of system parameters. Within the open-source community, cloud-based tuning has existed since 2015. For open-loop designs, DreaMed has an FDA-

approved physician-centered tuning platform called DreaMed Advisor Pro.⁸² The expansion of such automated tuning to AID systems may further impact personalization of these systems and help optimize control for users utilizing technology across a broader range of health care providers.

Conclusions

The future of AID certainly looks bright, with future work required to continue optimizing the technology, create streamlined regulatory pathways, and reduce disparities. For over a decade, there have been calls for moving beyond HbA1c as the only marker of benefit.⁸³ This call was partially answered by another metric of glycemic control, CGM TIR.⁸⁴ With AID allowing us to achieve consensus time-in-range criteria,⁸⁵ the time has now come to move beyond TIR and glycemia for expressing the gains provided by diabetes technology. Once glycemic goals are achieved, the focus must shift to technology that reduces diabetes effort and distress, enabling people with diabetes to focus on aspects of life outside of diabetes.

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