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Progress in Diabetes Technology: Developments in Insulin Pumps, Continuous Glucose Monitors, and Progress towards the Artificial Pancreas

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Type 1 diabetes (T1D) is one of the most common chronic diseases of childhood with an estimated prevalence of more than 166 000 cases in children younger than 20 years of age in the US in 2010.[1] The rate of new-onset diabetes also is increasing worldwide, with an increased incidence of 3%-5% per year.[2] In 1993 the Diabetes Control and Complications Trial established the benefit of intensive insulin therapy in reducing long-term complications, including retinopathy, nephropathy, and neuropathy.[3] Despite this now longstanding knowledge, vascular complications attributable to hyperglycemia remain a significant issue in the population with T1D, even in the young-adult population.[4,5] Recent evidence from the T1D Exchange clinic registry shows that during childhood mean hemoglobin A1c (HbA1c) remains above the target of 7.5% for all age groups, with a peak of 9.2% in the late teenage years.[6] This evidence points toward the urgent need for better therapeutic interventions to improve glycemic control across the pediatric population. Innovations in diabetes care are being pursued on many fronts, including education, behavioral interventions, pharmaceutical development, beta-cell transplantation, and immunomodulation to prevent autoimmune beta-cell destruction. Although these therapies aim to provide benefit now and more so in the future, many in the diabetes community believe that the most impactful near-term benefit will be achieved by innovation in the technologies used to manage diabetes.

Portable subcutaneous continuous insulin infusion (CSII) pumps first became possible in the early 1970s and achieved improved glycemic control in early studies.[7] Publication of the Diabetes Control and Complications Trial in 1993 demonstrated the importance of strict glycemic control and with it increased interest in the use of technology to minimize hyperglycemia without increasing hypoglycemia, still considered the greatest barrier to tight glucose control.[3,8] The late 1990s and early 2000s saw rapid expansion in design and availability of CSII systems as research showed improved outcomes with use of this technology.[9]

The concept of a mechanical artificial pancreas has evolved with development of CSII pump and continuous glucose monitoring (CGM) technology. Such a system involves multiple

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components, including a continuous insulin delivery device, glucose sensor, insulin dosing decision algorithm, and components necessary for device communication. There has been some interest in development of devices that can sample intravenous blood and/or deliver intravenous or intraperitoneal insulin, although the major focus of research and development has been on subcutaneous glucose monitoring and subcutaneous insulin delivery systems. This interest fueled development of CGM systems during the 1990s, with the first commercial CGM device being approved in 1999.[10–15] Continued improvements in CGM technology facilitated both direct benefits to the care of patients with T1D and paved the way toward the development of emerging artificial pancreas systems. In this medical progress report, we review recent advances in diabetes technology, including CSII pumps, CGM systems, and emerging artificial pancreas technology.

CSII Pumps

During the past 20 years, CSII pump therapy has evolved as a mainstay for many patients with T1D. Retrospective crossover studies from the mid-2000s showed that switching from multiple daily injection (MDI) to CSII pump therapy was associated with significant improvement in average HbA1c (0.25%-0.75% reduction after 1 year of pump therapy), fasting blood glucose, episodes of hypoglycemia, and blood glucose variability, without increased episodes of diabetic ketoacidosis (DKA).[16–19] Of note, the greatest benefits were shown for the patients with the greatest baseline HbA1c before initiation of pump therapy, suggesting that the idea of patients showing good control to “earn a pump” may not be an optimal strategy. It is also worth noting that not all studies on this subject have demonstrated improved diabetes control with CSII therapy, and randomized prospective studies have not shown a benefit in younger children.[20–22] No increases in DKA with pump use compared with injections are seen in registry data from 5 different countries in>54 000 youth with T1D[23] and children who have recurrent admissions to the hospital have a significant decrease in admissions when CSII therapy is initiated[24]

Studies on the durability of insulin pump use have continued to demonstrate superior glycemic control, lower insulin requirements, better health-related quality of life, and decreased hypoglycemic risk.[25,26] Among adolescents, the greatest benefits are seen for those patients who use the advanced features of the devices.[26]

Additional emerging research has investigated psychosocial factors involved with insulin pump therapy. Patients generally identify a desire for improved glycemic control and flexibility of insulin dosing as reasons for transitioning from MDI to CSII pump therapy.[27] Patient factors identified as predicting a greater rate of technology usage include a more active approach to diabetes care, realistic expectations of pump use, and recall of negative feelings at diabetes diagnosis.[28] Factors identified as predicting a lower rate of use include a passive approach to self-care, with a view of the pump as an automatic-cure all.[28] Detrimental aspects to pump use include body-image issues related to pump visibility, possible activity restrictions with pump use (eg, swimming with the pump), and concern over pump-site dysfunction and resultant DKA.[27,28]

Despite these noted benefits, <50% of patients in the US and Western Europe currently use insulin pumps. Data from 2011-2012 from 3 large clinical registries from the US and Western Europe shows that only 14% of patients in England and Wales, 41% of patients in Germany and Austria, and 47% of patients in the US were using insulin pumps.[23] The use of a pump was associated with an HbA1c 0.5% lower than not using a pump.

A particular challenge among providers who care for patients with T1D is keeping up with the rapidly changing face of diabetes technology. Not only do products offered by established technology companies change every few years, but there is a frequent flux of companies entering and exiting the marketplace of diabetes technology. Most providers do not believe that it is their place to dictate to their patients which device they should purchase or to call one device “the best.” Rather, we should present the spectrum of available options with the relative strengths and weaknesses. Here we present a review of commercially available CSII devices for sale in the US (Table I). This list is by no means exhaustive but provides a general overview and comparison of commercially available products at the time of submission of this review.

CGM

CGM development represents a vital component in advancement in the clinical utility of diabetes technology. The presence of accurate real-time glucose values allows patients and their providers exponentially more data for diabetes care decisions. CGM data provides 24-hour tracking of blood glucose values as opposed to a focused snap-shot data provided by intermittent blood glucose meter testing. The combination of patient use of CGM and CSII pump technology with the patient/parent making all decisions in insulin dosing is known as sensor-augmented pump (SAP) therapy.[29]

Early studies on the benefits of CGM use showed significant benefits for young adults but not for teens or younger children, mostly attributable to the low rates of use in the younger age groups.[30] Factors associated with greater rates of CGM use were patient age and frequency of blood glucose monitoring before beginning CGM and that frequency of CGM use predicted improvement in HbA1c.[31] Among those patients in the younger age groups who used CGM frequently (≥6 d/wk) benefits were similar to those in the older age groups.[32] Over an additional year, CGM use decreased with time in all age-groups, although frequent use of CGM was still associated with better HbA1c and reduced hypoglycemia in this cohort.[32–34]

Investigation into patients’ attitudes and beliefs surrounding CGM is an emerging area of research. These studies show positive themes of improved blood glucose control, reduced worry/uncertainty, and improved overnight control; negative themes include: uncertainty with interpreting CGM data, lack of device accuracy, intrusiveness of alarms, and discomfort with wearing the device.[35,36]

Despite the noted benefits, overall use of CGM in clinical practice still remains quite low. Recent T1D Exchange data shows increasing rates of CGM usage among participants in this cohort; as of 2015, 11% of participants had used CGM,[6] which is actually a 2% increase per

year from 9% in the 2013-2014 report[34] and a 7% rate of use among children in the 2010 report,[6] possibly indicating increased uptake over time with improving technology. Among those who had used CGM, 41% of participants discontinued its use within 1 year, although it should be noted that this study was performed on an older generation of CGMs.[34]

Emerging CGM technologies hold significant potential to reverse this trend. Early-generation CGM systems used devices with lower accuracy, larger size, fewer features, and more frequent calibration than the current models. There are currently only 2 CGM devices on the market in the US (Table II). An additional system, the Abbott FreeStyle Navigator, was sold previously in the US, and a new generation of this technology, the FreeStyle Libre, recently has been approved in Europe.[37]

An emerging feature of CGM technology is the availability of remote monitoring, which has been accelerated by parent/patient advocates such as the Nightscout movement.[38] This feature uses WiFi or cell phone signals to upload CGM data to cloud storage, enabling parents/caregivers to monitor a child's blood sugar while the child and parent are separated (eg, school and work). These products have now begun to move to commercial release, with the Dexcom Share approved in January 2015 and the Medtronic CareLink Connect with projected approval in late 2015. The technical limitations of the current CGM devices include the need for multiple daily calibrations, pressure induced attenuation of sensor signal,[39] interference from medications including acetaminophen,[40] and current 7-day approved life of the sensor. The next generation of CGM sensors are reported to be addressing all of these issues, most notably coming "out of the box" with accurate factory calibration as with current blood glucose meter strips, eliminating the need for finger-stick calibration. The Abbott FreeStyle Libre is approved for use in Europe without calibration.[37] Currently, the Food and Drug Administration does not approve of insulin dosing based solely on CGM data.

An additional limitation to more widespread CGM use is limited insurance coverage.[41] However, a recent economic analysis of SAP use in Sweden showed a favorable cost-effectiveness ratio of SAP, mostly attributable to reduced incidence of diabetes-related complications.[42] An older study from the Juvenile Diabetes Research Foundation (JDRF) also found long-term favorability of CGM use with an assumption of 2 fingerstick blood glucose tests per day.[43] A more recent analysis of cost-effectiveness analysis outlines the benefits of CGM beyond HbA1c to include lowering hypoglycemia rates and the costs associated with them, both psychological and financial.[41] Calibration-free devices could shift this equation towards the favorability of CGM as a cost-effective care tool as the cost of the sensor would be offset by decreased use of blood glucose meter test-strips. This shift in the cost-benefit equation would be most dramatically changed by approval for direct insulin dosing from CGM rather than from meter blood glucose values.

Artificial Pancreas Development

In 2006, the JDRF Artificial Pancreas project began, and in 2009 the JDRF outlined a 6 step-wise roadmap to development, refinement, and regulatory approval of a subcutaneous glucose monitoring and subcutaneous insulin delivery artificial pancreas system.[44,45] This

roadmap described successive steps from SAP therapy to systems involving sensor-directed suspension of insulin delivery to systems of hybrid and full closed-loop therapy and finally multihormone (eg, insulin and glucagon) therapy. Data exist on all steps of the 2009 roadmap summarized in this section, which demonstrate the feasibility of each.[46–55] Therefore, an updated roadmap has been introduced by Kowalski[55] to emphasize a bifurcated pathway to insulin only and bihormonal insulin systems. The Food and Drug Administration also has issued updated guidelines specifically for artificial pancreas development with an attempt to achieve "the least burdensome approach" toward artificial pancreas testing and approval.[56] They recommend that artificial pancreas systems be studied in 2 phases: first feasibility and then pivotal studies. Feasibility studies are underway and being completed at the time of this writing and pivotal studies are under design and implementation.

At the present time a step-1 commercial device (the Medtronic 530G system) with Threshold Suspend is available in the US and is helpful for patients with overnight hypoglycemia. This system successfully reduced overnight hypoglycemic events without producing rebound hyperglycemia in a recent phase 4 study.[57] A step-2 commercial device (the Medtronic 640G system) with predictive low-glucose suspend was approved in Australia and in Europe. Initial studies that use a different predictive low glucose suspend algorithm have shown substantial reduction in overnight hypoglycemia in patients as young as 4 years of age.[48,49,58] Step-3 devices with combined hypoglycemia and hyperglycemia minimizers are currently under phase 3 study.[59]

Devices consisting of hybrid closed-loop systems, fully automated closed-loop systems, and dual-hormonal systems are all under development at various stages of clinical testing at roughly a dozen centers around the world. The pathway to commercial approval for these advanced devices generally starts with in silico testing with computer-based compartment models of glucose response to insulin, followed by testing in a hospital setting, then in a controlled environment outside the hospital (eg, hotels and diabetes camps), and finally testing in the home environments.

Because of the pharmacokinetic limitations of current rapid acting insulins, closed-loop systems generally perform better during periods of fasting (such as overnight) and still have difficulty with the glycemic excursion of unannounced meals. Hybrid systems involve manual bolusing for meals and also use algorithm determined insulin delivery based on sensor glucose levels. These systems are especially effective overnight.[52,60,61] A full closed-loop system would not require the user to enter meal boluses and would deliver all insulin without the need for the patient to enter food or exercise events.

A fundamental aspect of any artificial pancreas system is the control algorithm responsible for making dynamic insulin dosing adjustments in real-time. The theory for artificial pancreas algorithms arises from the discipline of control theory and dynamical systems.[62,63] Control theory arises from ideas in mathematics and is a fundamental tool in many engineering disciplines, including aerospace, mechanical, chemical, and electrical and computer engineering. A comprehensive review of the engineering of artificial pancreas algorithms was recently published by Doyle et al.[64]

Groups around the world generally are using 3 different control systems for Closed Loop (CL) therapy: proportional-integral-derivative (PID) control, model predictive control (MPC), and fuzzy logic control. PID control is probably the most basic form of a control system. At each point in time the controller assesses how far the current glucose is from the desired glucose (proportional), the rate of change in glucose (derivative), and how long the glucose has remained above or below target (integral), and then uses a weighted sum of these factors to determine an insulin dose for that point in time.[52,65] MPC relies on the development of a complex multicompartment model via a series of differential equations. This model is then used to predict the appropriate dosing action for a fixed time interval (eg, 5-15 minutes), after which time the system is reassessed and the appropriate model selected for the next time interval.[66,67] Fuzzy logic control uses a series of "fuzzy" logical decision rules based on the current glucose and the direction and rate of change of the glucose to make reasoned decisions on insulin doses.[68,69] A fuzzy logic controller attempts to imitate the reasoning of a diabetes clinician whereby an expert clinician's dosing expertise is codified in terms of dosing rules based on different glucose circumstances such as glucose level, glucose rate of change, and glucose acceleration.[70] In addition to commercial development of artificial pancreas systems, patient/parent-driven development is also occurring in a manner similar to the Nightscout movement (http://www.nightscoutfoundation.org/about) with CGM. Bigfoot Biomedical is a startup company with a CL algorithm developed by parents of children with T1D that intends to drive artificial pancreas development rapidly forward.[71] Do It Yourself Pancreas System started as a couple hacking the CGM to make the alarms louder and has now progressed into a patient-driven artificial pancreas system that uses Open Source artificial pancreas code.[72]

Current research on CL systems demonstrate an overall common theme of successful control of overnight blood glucose with values in target range 70%-100% of the time, but there is some difficulty in preventing postmeal glycemic excursions with unannounced meals. A summary article of CL research was published recently by Shah et al.[73] Research on MPC systems has shown increased time in normal range without increased hyperglycemia in hospital settings when compared with MDI and SAP therapy,[74–79] and has now shown reduced hypoglycemia and increased time in range in early camp and out-patient settings.[50,61,79–81] PID systems have shown improved time in range with reduced hypoglycemia in hospital and camp settings.[60,82] Fuzzy logic systems have shown increased time in range with reduced hypoglycemia compared with SAP in outpatient settings.[83] The "Bionic Pancreas" provides the replacement of both insulin and glucagon.[84,85] This system has been used successfully in a hotel setting and in diabetes camps, achieving an average glucose in adults/adolescents of 138/138 mg/dL with 4.1/6.1% of readings <70 mg/dL. Studies combining closed-loop artificial pancreas technology with adjuvant diabetes medication also are underway. These studies investigate the role of adjuvant medications such as sodium-glucose linked transporter 2 inhibitors, combined sodium-glucose linked transporter 1/2 inhibitors, amylin analogues, glucagon-like peptide-1 agonists, and inhaled insulin. Studies combining these agents with diabetes technology show early promise to help mitigate postprandial hyperglycemia.[86–90]

Barriers on the Pathway to Clinical Use

There are several commonly cited technical barriers to full implementation of CL technology. These include: (1) the need for more accurate CGM devices with less calibration, better accuracy, and longer life-span; (2) the need for “ultra-rapid” insulins that have a faster onset, more rapid peak, and shorter duration of action to more closely replicate pancreatic portal insulin onset and duration of action particularly as it pertains to preventing meal-time glycemic excursions and postprandial hyperglycemia; (3) the continued need for algorithm refinement and improvement possibly including features for exercise, stress, sleep, and illness; and (4) the need for continued improvement in the user interface which includes: (a) the device interfaces with the user; (b) device connectivity between sensors, pumps, the controller, and the cloud; and (c) the sites at which devices are worn on the skin, which includes tape, insertion sites, the number of devices worn, and the length of time that they can be worn. An additional technical barrier for dual-hormone (insulin and glucagon) systems is the lack of a commercially available aqueous stable formulation of glucagon. Currently commercially available glucagon forms fibrils in aqueous solution and is therefore only usable for 24 hours after reconstitution. In response to this limitation commercial development is underway on stable aqueous and nonaqueous glucagon formulations.[91,92]

One of the major focuses on future technological development must be the need to reduce the burden of T1D. The concept of reduced burden has begun to emerge in the technology community and its success will likely be linked with the future uptake and success of artificial pancreas technology.[93] In his recent pathway update, Kowalski[55] addresses these barriers as well as the needs for patient and health care provider acceptance and payer coverage of emerging diabetes technology. The concept of cost-effectiveness of advanced diabetes technologies has also begun to be studied. Although upfront costs for these systems will be significant, predictive economic analysis has shown that reduced hospital costs from visits to the emergency department and admissions caused by hypoglycemia and long-term complication reduction from improved HbA1c show a cost benefit for advanced diabetes technology including artificial pancreas systems.[41,94] Cost-effectiveness of these systems is critical as, the ultimate metric for success of artificial pancreas systems will be based on their widespread use and how they improve quality of life, reduce stress, and improve outcomes for all patients with diabetes.

Conclusions

All steps in the artificial pancreas pathway have been shown to be feasible. Studies are now moving from preliminary controlled in-patient settings to pivotal real-world outpatient settings. Continued development of these technologies must focus on patient-centered needs and reducing the global burden of T1D on these patients. With this focus, diabetes technology promises to reduce burden and improve clinical outcomes for a wide spectrum of patients with diabetes in the near future.

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Glossary

CGM	Continuous glucose monitoring
CSII	Continuous insulin infusion
DKA	Diabetic ketoacidosis
HbA1c	Hemoglobin A1c
JDRF	Juvenile Diabetes Research Foundation
MDI	Multiple daily injection
MPC	Multiple daily injection
PID	Proportional-integral-derivative
SAP	Sensor-augmented pump
T1D	Type 1 diabetes

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Table I.

Commercially available insulin pumps, US, 2015

Pump brand	CGM pairing	CGM on-screen	Low-glucose suspend	Color screen	Basal increments, U/hr	Basal intervals, min	Minimum bolus increments, U	Tubing connection	Blood glucose meter pairing
Animas Vibe (Animas Diabetes, West Chester, Pennsylvania)	Yes; Dexcom G4	Yes	No	Yes	0.025	30	0.05	Luerlock	None
Medtronic MiniMed Paradigm Revel 530G (Medtronic Diabetes, Northridge, California)	Yes; Enlite 2	Yes	Yes; Threshold Suspend	No	0.025	30	0.025	Medtronic	Bayer Contor Next
Insulet OmniPod (Insulet, Billerica, Massachusetts)	Under development; Dexcom	N/A	No	Yes	0.05	30	0.05	N/A - Tubeless	Freestyle Integrated into PDM
Roche Accu-Chek Spirit Combo (Roche Diagnostics, Indianapolis, Indiana)	Under development	N/A	No	No	0.01	60	0.1	Luer lock	Accu-Chek Aviva Combo
Tandem t:slim (Tandem Diabetes Care, San Diego, California)	Yes; Dexcom G4	Yes	No	Yes; Touch	0.001	1	0.01	Luer lock	None

N/A, not available; *PDM*, Personal Diabetes Manager.

Table II.

Commercially available CGMs, US, 2015

CGM brand	Pump pairing	Sensor life, d	Angle of insertion, degrees	Warm-up time, h	Calibration	Glucose display frequency, min	Directional trend display	Remote monitoring available
Dexcom G4 PLATINUM and G5 Mobile (Dexcom, San Diego, California)	Own receiver; Animas Vibe and t:slim; under development-OmniPod	7	45	2	Every 12 h	5	Yes	Dexcom Share
Medtronic Enlite (Medtronic Diabetes, Northridge, California)	Medtronic Paradigm	6	90	2	Every 12 h	5	Yes	CareLink Connect