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]

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

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 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

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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]

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	Luer lock	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.