COMMENTARY

Will the First Approved Automated Insulin Delivery System Be a Game-Changer in Type 1 Diabetes Management?

Jessica R. Castle, MD

IN A PERSON WITHOUT DIABETES, glucose is maintained in a very narrow range. To accomplish this, beta cells have a clever mechanism by which they respond to rising glucose levels with increased insulin secretion. As glucose levels rise, more glucose is metabolized by the beta cell, which in turn stimulates insulin secretion. In contrast, people with type 1 diabetes (T1D) must rely on insulin delivery via injections or via an insulin pump. As stand-alone devices, insulin pumps lack an automated feedback mechanism by which to adjust insulin delivery rates. They have set basal rate profiles and rely on users to input grams of carbohydrate and glucose values to determine insulin bolus amounts.

The commercial availability of continuous glucose monitoring (CGM) starting in 2000 dramatically changed the options available to manage diabetes.¹ These devices allow for viewing of sensed glucose values in real time. But what has been lacking up until recently is the availability of automated insulin delivery systems, which modulate insulin delivery in response to sensed glucose values. Often these systems are termed artificial pancreas systems, although this term is somewhat misleading as these systems typically only deliver insulin, do not mimic the other functions of the pancreas, and lack many inputs that control hormone secretion of the normal human pancreas.²

The first system to provide some form of insulin automation was the Medtronic 530G with Enlite. This system includes a threshold suspend feature, such that when the sensed glucose value drops to a certain threshold (settable between 60 and 90 mg/dL), the system alarms. If the user does not respond to the alarm, such as while asleep, insulin delivery is suspended for 2 h, or until manually resumed. In a study of 247 patients with documented nocturnal hypoglycemia, the threshold suspend feature significantly reduced hypoglycemia; the percent time of the sensor reading <50 mg/dL was decreased by 57%.³ However, the Medtronic 530G system was not designed to prevent hypoglycemia, only to reduce the severity and duration of hypoglycemia once it occurs. The Medtronic 640G system was designed to prevent hypoglycemia using a predictive low-glucose suspend

(PLGS) feature. With this feature, when hypoglycemia is predicted using a linear prediction, insulin is automatically suspended and then resumed again once the sensed glucose is predicted to rise above a set threshold.⁴ In a study of children with T1D, use of PLGS reduced the percentage of time with sensed glucose values <70 mg/dL by 54% in children 11–14 years of age (10.1% on control nights to 4.6% on intervention nights) and by 50% in children 4–10 years of age (6.2% on control nights to 3.1% on intervention nights).⁵

Although the 530G and 640G systems significantly reduce hypoglycemia, they were not designed to address hyperglycemia. Uncontrolled diabetes remains the leading cause of kidney failure, lower-limb amputations, and adult-onset blindness.⁶ In data collected by the T1D Exchange, the vast majority of youth⁷ and adults⁸ do not meet A1C targets set forth by the American Diabetes Association. To date, there has been an unmet need to address the risk of hyperglycemia in people with T1D to reduce the risk of diabetes-related complications. In 2016, the Food and Drug Administration (FDA) approved the Medtronic 670G system with Enlite. This is the first system approved by the FDA that automates insulin delivery between meal and correction boluses both to increase insulin delivery for hyperglycemia and reduce insulin delivery for impending hypoglycemia.

The article by Garg et al. published in this issue of *Diabetes Technology & Therapeutics* describes the results of the pivotal trial using the Medtronic 670G system.⁹ This trial included 94 adults and 30 adolescents who wore the system for 2 weeks without insulin automation, and the results from this period were then compared with 3 months using the 670G system with insulin automation enabled, termed Auto Mode. Auto Mode was enabled a median of 18.2 h/day for adolescents and 21.1 h/day for adults. Use of Auto Mode increased insulin delivery modestly, from 55.6 to 60.2 U/day in adolescents and from 44.9 to 47.9 U/day in adults. Compared with baseline, A1C dropped on average by 0.7% in adolescents and by 0.5% in adults ($P < 0.001$). Time in hypoglycemia and time in hyperglycemia were reduced in both

groups (percentage of sensor values ≤ 70 mg/dL decreased from 4.2% to 2.8% in adolescents and from 6.4% to 3.4% in adults and percentage of sensor values > 300 mg/dL decreased from 3.8% to 2.8% in adolescents and from 1.8% to 1.3% in adults).

This pivotal trial was designed to be a safety trial. It did not include a randomized control, and therefore, the results must be interpreted cautiously. The results clearly showed the 670G systems to be effective in managing T1D with a low rate of hypoglycemia within the study design. However, it is unknown to what degree the reduction in A1C is attributable to the use of the CGM compared with the insulin automation. It is now well established that the use of CGM improves glucose control both with insulin pump use and with the use of multiple daily injections.^{10,11}

Patients used CGM during the run-in period making the comparison of percentage of time of CGM values in particular ranges, such as time in hypoglycemia, more comparable, but there is a period of learning with CGM that may not have been complete by the end of the 2-week period. Additionally, the use of the 670G system in this study did not approximate a real-life scenario. For example, during the first 2 weeks of system use, participants downloaded their devices daily for data review and setting adjustments. These types of interventions are appropriate for investigations of a new device but are not replicated under normal circumstances. Therefore, the study outcomes may not be directly applicable to use in the outpatient settings.

Exercise and meals continue to be a challenge to manage even with insulin automation.¹² The challenge stems from that insulin delivered subcutaneous has a delayed onset and offset of action.¹³ Premeal and correction boluses are still required with the 670G system. Therefore, there still remains a burden on the patient to count carbohydrates. One would expect that those who miss a meal bolus, however, will be better off using an automated insulin delivery system that adjusts the insulin delivery rate in response to hyperglycemia. Exercise is a challenge because of the potential sharp drop in glucose related to increased glucose disposal in working muscles and increased insulin sensitivity.¹⁴ The 670G system includes the ability to increase the glucose target to 150 mg/dL to reduce the risk of exercise-related hypoglycemia. Although, because of the delayed action of subcutaneous insulin, even shutting off insulin at the start of exercise may not prevent hypoglycemia.¹⁵

With the approval of the 670G system, automated insulin delivery is now soon to be available to patients. This is after many years of effort on the part of patients who have participated in studies, organizations such as JDRF, Helmsley Charitable Trust, and the National Institutes of Health (NIH) who have funded many of these research efforts, academic researchers, and medical device companies. There are very likely more automated insulin delivery systems soon to be available. Tandem, Insulet, and Animas, all makers of insulin pumps, have undertaken the development of an automated insulin delivery system in some form.¹⁶ The NIH has funded multiple large clinical trials testing automated insulin delivery systems, including at the University of Virginia and University of Cambridge as well as an automated insulin and glucagon delivery system at Boston University.¹⁷

Companies have been developed for the sole purpose of bringing an automated insulin delivery system to market for

patients, including BigFoot Biomedical. Automated insulin delivery is likely soon to be the new standard of care for managing T1D. Providers and patients alike are hopeful that these systems will prove to reduce the burden of diabetes and greatly reduce the risk of significant hyperglycemia and hypoglycemia.

Author Disclosure Statement

J.R.C. has a financial interest in Pacific Diabetes Technologies, Inc., a company that may have a commercial interest in the results of this research and technology. This potential conflict of interest has been reviewed and managed by OHSU. In addition, J.R.C. reports research support from Dexcom and Tandem Diabetes Care outside the submitted work. The time for J.R.C. to prepare this article was supported by grant 1DP3DK101044-01 from NIH/NIDDK.

References

1. Rodbard D: Continuous glucose monitoring: a review of successes, challenges, and opportunities. *Diabetes Technol Ther* 2016;18 Suppl 2:S3–S13.
2. Thabit H, Hovorka R: Coming of age: the artificial pancreas for type 1 diabetes. *Diabetologia* 2016;59:1795–1805.
3. Bergenstal RM, Klonoff DC, Garg SK, et al.: Threshold-based insulin-pump interruption for reduction of hypoglycemia. *N Engl J Med* 2013;369:224–232.
4. Howsmon D, Bequette BW: Hypo- and hyperglycemic alarms: devices and algorithms. *J Diabetes Sci Technol* 2015;9:1126–1137.
5. Buckingham BA, Raghinaru D, Cameron F, et al.: Predictive low-glucose insulin suspension reduces duration of nocturnal hypoglycemia in children without increasing ketosis. *Diabetes Care* 2015;38:1197–1204.
6. Centers for Disease Control and Prevention. *Diabetes Report Card 2014*. Atlanta, GA: Centers for Disease Control and Prevention, US Dept of Health and Human Services, 2015.
7. Wood JR, Miller KM, Maahs DM, et al.: Most youth with type 1 diabetes in the T1D exchange clinic registry do not meet American Diabetes Association or International Society for Pediatric and Adolescent Diabetes clinical guidelines. *Diabetes Care* 2013;36:2035–2037.
8. Miller KM, Beck RW, Bergenstal RM, et al.: Evidence of a strong association between frequency of self-monitoring of blood glucose and hemoglobin A1c levels in T1D exchange clinic registry participants. *Diabetes Care* 2013;36:2009–2014.
9. Garg SK, Weinzimer SA, Tamborlane WV, et al.: Glucose outcomes with the in-home use of a hybrid closed-loop insulin delivery system in adolescents and adults with type 1 diabetes. *Diabetes Technol Ther* 2017;19:155–163.
10. Beck RW, Riddlesworth T, Ruedy K, et al.: Effect of continuous glucose monitoring on glycemic control in adults with type 1 diabetes using insulin injections: the DIAMOND randomized clinical trial. *JAMA* 2017;317:371–378.
11. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group, Tamborlane WV, Beck RW, et al.: Continuous glucose monitoring and intensive treatment of type 1 diabetes. *N Engl J Med* 2008;359:1464–1476.
12. Bequette BW: Challenges and recent progress in the development of a closed-loop artificial pancreas. *Annu Rev Control* 2012;36:255–266.

13. Heinemann L, Weyer C, Rauhaus M, et al.: Variability of the metabolic effect of soluble insulin and the rapid-acting insulin analog insulin aspart. *Diabetes Care* 1998;21:1910–1914.
14. Colberg SR, Laan R, Dassau E, et al.: Physical activity and type 1 diabetes: time for a rewire? *J Diabetes Sci Technol* 2015;9:609–618.
15. Diabetes Research in Children Network Study G, Tsalikian E, Kollman C, et al.: Prevention of hypoglycemia during exercise in children with type 1 diabetes by suspending basal insulin. *Diabetes Care* 2006;29:2200–2204.
16. <https://www.clinicaltrials.gov> (accessed February 8, 2017).
17. Four pivotal NIH-funded artificial pancreas research efforts begin. 2017. <https://www.nih.gov/news-events/news-releases/four-pivotal-nih-funded-artificial-pancreas-research-efforts-begin> (accessed February 8, 2017).

Address correspondence to:

Jessica R. Castle, MD

Mail Code OP05DC

3181 SW Sam Jackson Park Road

Portland, OR 97239

E-mail: castleje@ohsu.edu