10TH ANNIVERSARY SERIES

Advances in artificial pancreas systems

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The artificial pancreas for managing type 1 diabetes has progressed from research into clinical practice, revealing areas for future advancements.

In type 1 diabetes, immune-mediated destruction of the pancreatic β cells causes insufficient insulin production and life-long dependency on exogenous insulin administration. In health, insulin is released in response to elevated blood glucose and facilitates glucose transport from the blood into cells throughout the body. To mimic the healthy pancreas, basal exogenous insulin administration replicates the background insulin produced by the pancreas, and additional insulin boluses are required at mealtimes, when glucose concentrations rise in response to carbohydrate consumption. Maintaining blood glucose concentrations as close as possible to the nondiabetic range is essential for people with type 1 diabetes to avoid the long-term complications of high blood glucose concentrations (hyperglycemia). Although intensive insulin therapy, with multiple daily insulin injections or insulin pump therapy and frequent blood glucose measurements, is routinely applied to manage type 1 diabetes, many people fail to achieve adequate glycemic control due to limiting low glucose concentrations (hypoglycemia). As the burden of diabetes self-management remains high, there is a growing need for devices that continuously monitor glucose concentrations and automatically adjust insulin delivery rates—the so-called "artificial pancreas"—to help maintain blood glucose in a healthy range. In this Focus article, the third in a special series to celebrate the 10th anniversary of *Science Translational Medicine*, we discuss advances in artificial pancreas systems achieved over the past decade and considerations for continued progress toward widespread clinical adoption. There has been much progress since *Science Translational Medicine* published a study by El-Khatib *et al.* (*1*) in 2010, showing that a bi-hormonal artificial pancreas, automatically delivering insulin and glucagon, was a feasible approach to achieving near-normal glucose concentrations in people with type 1 diabetes.

THE ARTIFICIAL PANCREAS

Automated insulin delivery has long been an enticing goal to accommodate variable hour-to-hour and day-to-day insulin requirements while also reducing the burden of self-care. Improvements in the accuracy and reliability of continuous glucose monitors (small sensors worn subcutaneously that continuously measure interstitial glucose concentrations) have enabled progressive development and recent adoption of automated insulin delivery systems in clinical practice. The simplest automated insulin delivery system suspends insulin delivery when sensor-detected glucose concentrations cross a prespecified threshold (low glucose suspend) or are predicted to cross the prespecified threshold within a certain time period (predictive low glucose suspend). Closed-loop insulin delivery systems, which increase and decrease insulin delivery to achieve target glucose concentrations, are more sophisticated. An adaptive control algorithm (often personalized initially using body weight and/or total daily insulin dose and then based on individual sensor glucose data) automatically and continuously adjusts insulin delivery in response to sensor-detected glucose concentrations. An insulin pump delivers insulin via a subcutaneous cannula to the user; the insulin infusion rate is directed by the algorithm hosted on a hand-held device such as a smartphone or on the insulin pump itself, which receives and processes continuous glucose monitoring data (Fig. 1).

Both single-hormone systems (delivering insulin only) and dual-hormone systems (delivering insulin and glucagon or another hormone) are being pursued clinically. The addition of glucagon has the potential to further alleviate the risk of hypoglycemia but increases the system's complexity with separate drug reservoirs and infusion sets. From a patient perspective, the ideal closed-loop system requires minimal user interaction, device burden, and inconvenience while achieving optimal glucose control. Fully closed-loop systems that detect and automatically dose insulin for meals have been attempted, but glucose control is compromised because of delays in the absorption of subcutaneous rapid-acting insulin analogs. Therefore, most closed-loop systems adopt a hybrid approach, requiring manual administration of insulin boluses for meals. Simplified meal announcements using qualitative estimates of meal size rather than accurate carbohydrate counting have been used to attain reasonable post-prandial glucose control.

In 2010, a study by El-Khatib *et al.* (*1*) published in *Science and Translational Medicine* sparked interest in the development of dual-hormone closed-loop systems. Algorithm-directed subcutaneous delivery of insulin lispro (rapid acting insulin analog) and glucagon in 11 adults for a period of 27 hours under supervised conditions in a clinical research facility achieved near-normal mean blood glucose concentrations with minimal hypoglycemia. The algorithm did not receive meal announcements but, due to the delay in insulin lispro absorption, led to delivery of more insulin than required, using glucagon delivery to mitigate insulin overdelivery. An adjustment to account for variability in insulin lispro kinetics led to improved glucose control. Concurrently, several other groups demonstrated feasibility and safety of automated insulin delivery using single-hormone closed-loop prototypes in supervised settings. A series of randomized crossover clinical studies undertaken in Cambridge, UK, demonstrated that closed-loop insulin delivery could increase the duration the glucose concentration was within target glucose range while reducing time spent in hypoglycemia.

SINGLE-HORMONE CLOSED-LOOP STUDIES

The first study exploring the feasibility of prolonged use of a single-hormone artificial pancreas system overnight in the home setting compared closed-loop insulin delivery with sensor-augmented pump therapy in 24 subjects over 6 weeks with remote monitoring (availability of glucose data to health care

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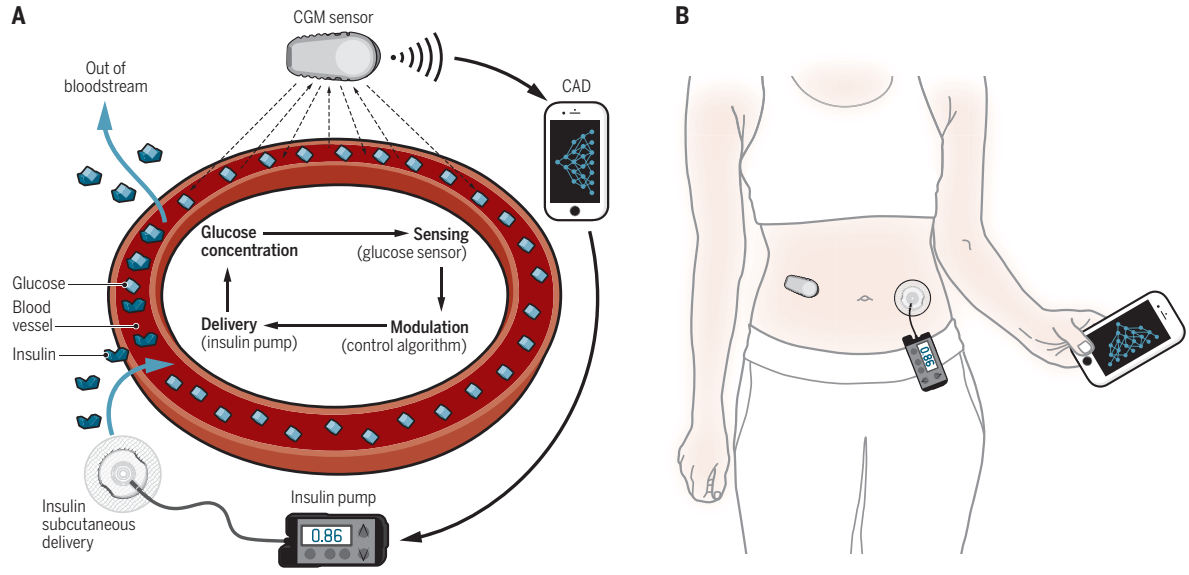

Fig. 1. Closed-loop artificial pancreas systems. (**A**) Diagram depicting closed-loop insulin delivery. A continuous glucose monitor (CGM) worn subcutaneously transmits information about interstitial glucose concentrations to a smartphone or other control algorithm device (CAD), which hosts a control algorithm that translates information from the CGM and computes the amount of insulin to deliver. An insulin pump delivers rapid-acting insulin analog subcutaneously. Insulin delivery is modulated in real time by the control algorithm. Communication between system components is wireless. (**B**) Schematic depicting where the components of a closed-loop insulin delivery system may be worn and held by a human subject with type 1 diabetes.

professionals not in the immediate vicinity of the user) (*2*). Closed-loop control overnight reduced time in hypoglycemia and increased time in the target glucose range compared with control nights. This demonstrated the feasibility of using closed-loop insulin delivery in real-world settings.

The efficacy and safety of closed-loop glucose control in the outpatient setting has been demonstrated in multiple studies using different closed-loop prototypes and in meta-analysis. The proportion of time spent in target glucose range (between 3.9 and 10 mM) was higher with closed-loop compared with control therapy, both overnight and over a 24-hour period (*3*). Closed-loop insulin delivery reduced the proportion of time with sensor glucose above 10 mM and the time below 3.9 mM over 24 hours; closed-loop systems also decreased glycated hemoglobin by 0.3%.

Key to demonstrating robustness of closed-loop technology and generalizability of therapeutic benefits is the inclusion of a wide range of people with type 1 diabetes (different ages, baseline glycemic control, and backgrounds) in studies. In a recent multinational randomized controlled trial, 86 children and adults with suboptimal glycemic control (glycated hemoglobin, 7.5 to 10.0%) using insulin pump therapy received either hybrid closed-loop or sensor-augmented pump therapy over 12 weeks under free-living conditions (*4*). The proportion of time that glucose was within target was higher with closed-loop compared with pump therapy (65% versus 54%, respectively), and time in hypoglycemia was also reduced. Glycated hemoglobin was reduced by 0.4% with closed-loop use compared with 0.1% in the control group (*4*).

The first commercially available artificial pancreas, a hybrid single-hormone closed-loop system (MiniMed 670G Insulin Pump System, Medtronic), is approved for use in people aged 7 years and older and reportedly has more than 100,000 users. The pivotal study designed to demonstrate safety of this first-generation closed-loop system, a single-arm study without a control group, involved 124 people aged 14 to 75 years who used the closed-loop system initially during a 6-day hotel stay and then unsupervised in free-living conditions for 3 months (*5*). Over 12,389 patient days, there were no episodes of severe hypoglycemia or ketoacidosis. Limitations to the system include frequent exits from closed-loop (auto) mode due to prolonged hyperglycemia, loss of sensor glucose data, or insulin delivery above or below calculated safety levels. Usage of auto mode has also been reported to decline over time in users, and reasons for this need to be explored. Safety of this technology in real-world settings supports clinical adoption of hybrid closed-loop systems for people with type 1 diabetes, and future generations of this system with modified features are under development. Several other companies are also developing commercial single-hormone closed-loop systems, including Insulet, Bigfoot Biomedical, Beta Bionics, Tandem Diabetes Care, Roche, and Diabeloop. These systems use different combinations of technologies and algorithms and are currently in clinical trials. Regulatory support for interoperability has been orchestrated by the FDA (U.S. Food and Drug Administration), defining a new type of devices such as iCGM (interoperable CGM) and ACE (alternate controller enabled) pumps.

The #WeAreNotWaiting diabetes community has developed alternative noncommercial artificial pancreas systems. The OpenAPS (Open Artificial Pancreas System) movement includes individuals building their own do-it-yourself (DIY) closed-loop systems from commercially available insulin pumps (although sometimes out of warranty), continuous glucose monitoring devices, and an open source algorithm. DIY systems benefit from a fast innovation cycle and customization alongside transparency of algorithm decision-making; these systems appeal to an increasing population of people with type 1 diabetes, with more than 1000 users to date worldwide (*6*). The responsibility of health care professionals in supporting users of these non-regulatory approved systems remains controversial.

DUAL-HORMONE CLOSED-LOOP SYSTEMS

Dual-hormone closed-loop systems have progressed since the key initial study in 2010 (*1*). In the first free-living remotely monitored

crossover study, dual-hormone hybrid closed-loop control was compared to standard insulin pump therapy in 52 adolescents and adults for 5 days with close supervision (*7*). Among adults, mean glucose was lower with closed-loop, time in target glucose range was greater (80% versus 59%), and time in hypoglycemia was reduced (4.1% versus 7.3%) compared to standard pump therapy. Similar glycemic benefits were observed in an outpatient study of 19 pre-adolescent children aged 6 to 11 years in a diabetes camp setting (residential camp where specialist staff provide supervision to facilitate a medically safe environment) (*8*). The dual-hormone closed-loop system was associated with lower mean glucose, increased time in target range, and less time in hypoglycemia with fewer rescue carbohydrates than standard pump therapy. A study of dual hormone closed-loop control in the home setting with remote monitoring in 43 adults over 11 days using optional meal announcements without carbohydrate counting showed increased time in target glucose range and reduced hypoglycemia compared to insulin pump therapy (*9*). Meta-analyses report that addition of glucagon is associated with a greater increase in time in target glucose range and a greater decrease in time in hypoglycemia versus comparator, compared with single-hormone systems (*3*).

The appeal of dual-hormone systems to reduce the risk of hypoglycemia and achieve more physiologic glucose control is self-evident; however, progress has been limited because of lack of commercially available room-temperature-stable glucagon, device complexity, and the short duration and small size of clinical studies. Currently, there are no commercially available dual-hormone closed-loop systems. Companies including Beta Bionics in collaboration with Xeris Pharmaceuticals, Zealand Pharma, and Lilly are developing such systems.

PSYCHOSOCIAL IMPACT OF CLOSED-LOOP SYSTEMS

Understanding expectations and experiences of users of closed-loop systems is important for effective and sustainable system usage. Individuals may perceive the same technology differently due to previous experiences and general psychological attitudes. The impact of closed-loop technology on quality-of-life measures has been explored in several studies (*10*).

Interviews of closed-loop users generally report positive user experience. Benefits include improved glucose control leading to reassurance and reduced anxiety, improved sleep and confidence due to improved overnight glucose control, relaxed eating habits, and "time off" from the demands of diabetes. Challenges include technical difficulties, alarm intrusiveness, and size of equipment in addition to variable trust and difficulties incorporating closed-loop systems into activities of daily life (exercise and bathing). Low-frequency users, with regard to time spent using the closed-loop system, reported little benefit during the day and more interruptions to their daily lives from alarms. Most participants in closed-loop studies reported that they would personally continue using or would recommend closed-loop therapy to a friend or relative if available because the clinical benefits outweigh system imperfections. Exploring the psychosocial aspects of closed-loop technology and related training among health care professionals will be instrumental in ensuring that clinical benefits are realized in routine care.

LOOKING TO THE FUTURE

Improvements in closed-loop system components are likely to enhance performance and user experience. Noncalibrating continuous glucose monitoring devices with increased accuracy and longer wear time, and algorithms incorporated into insulin pumps or as an application on a smartphone, will reduce device burden. Flexibility to choose different combinations of "open protocol" devices for automated insulin delivery, which allow seamless and secure connectivity with other devices, will improve user choice and experience and has been supported by a JDRF initiative to expedite regulatory approval of interoperable devices.

Ultrafast-acting insulin analogs or adjuncts that reduce postprandial glucose responses may facilitate progress from hybrid closed-loop systems requiring prandial boluses to fully automated systems. Algorithms integrating multiple signals, including measures of activity, may more accurately reflect rapidly changing insulin requirements than sensor glucose input alone.

Remote monitoring systems (for example, Dexcom Share) allow glucose data sharing among selected individuals and will likely increase appeal and acceptability of closed-loop control. Data management platforms such as Diasend/Glooko will be important in making data from closed-loop systems readily accessible to both users and health care professionals and for supporting optimal usage of this technology. Clinical studies applying closed-loop to particular cohorts of individuals with type 1 diabetes will be important in determining those who can benefit most from closed-loop technology and will provide key evidence to support reimbursement by health care providers.

The artificial pancreas for people with type 1 diabetes has been successfully translated from research into clinical practice. Future closed-loop systems will likely improve performance and acceptability. Widespread adoption of closed-loop systems as the standard of care will require a clear understanding of the training needs of both users and health care professionals to ensure successful implementation. Cost-effective analyses are required for health care systems to support reimbursement of this technology.

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