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Opportunities and challenges in closed-loop systems in type 1 diabetes

Leah M. Wilson, Peter G. Jacobs, Michael C. Riddell, Dessi P. Zaharieva, Jessica R. Castle

Commercial automated insulin delivery therapy can improve glucose outcomes by increasing glucose time-in-range (3·9–10·0 mmol/L; 70–180 mg/dL) and reducing hypoglycaemia (<3·9 mmol/L; <70 mg/dL) in people with type 1 diabetes. Commercial closed-loop systems have shown modest improvement in percentage time-in-range, with an increase of 5 percentage points for MiniMed 670G [1] and of 10 percentage points for Control-IQ [2] compared with open-loop therapy. New developments with closed-loop systems are likely to enable further improvements in glucose outcomes while reducing user burden for individuals able to access closed-loop systems. These developments are focused on addressing deficiencies with current closed-loop systems by, for example, reducing or eliminating the requirement of prandial insulin dosing, overcoming the slow kinetics of subcutaneous insulin compared with endogenous insulin production, and improving the handling of insulin before, during, and after exercise. These advances will ideally lead to improved performance and reduced patient burden, and enable more widespread usage.

Current closed-loop systems are hybrid systems. These systems are not fully automated and require user estimation of carbohydrate intake and manual insulin dosing before a meal. Pre-meal insulin dosing is important to prevent marked hyperglycaemia due to the slow kinetics of subcutaneous insulin absorption into the plasma, as compared with the rapid effects of endogenous insulin and incretin in normal postprandial physiology. An automated insulin control algorithm that is unaware of a meal will attempt to compensate for the postprandial hyperglycaemia by delivering additional insulin, which can potentially lead to subsequent hypoglycaemia following the meal. Compounding this problem is the fact that people might forget to dose prandial insulin entirely, dose the insulin after a meal, or misestimate carbohydrate

consumption, which is common [3]. Future closed-loop systems might benefit from a fully automated control algorithm that uses artificial intelligence to detect when a meal is consumed and deliver prandial insulin once detection occurs. This system will not replicate normal physiology, but has the potential to benefit those living with type 1 diabetes who have to consistently take prandial insulin. For example, an algorithm that detects a meal can either automatically deliver a proportion of the intended prandial insulin or prompt the user to dose.

Closed-loop systems are dependent on accurate continuous glucose monitoring, which measures interstitial glucose, to drive insulin delivery. The accuracy of continuous glucose monitoring has improved remarkably over the past 15 years and there is now an integrated continuous glucose monitoring standard for use in closed-loop systems. However, there are still some problems to overcome. There is inherently some delay in interstitial glucose measurements as compared with actual plasma glucose concentrations. This delay can be more pronounced during exercise and after meals when glucose concentrations are changing rapidly. However, data have shown that the accuracy of continuous glucose monitoring during exercise can be high [4]. In addition, physically pressing on a continuous glucose monitoring device, such as lying on it while sleeping, can cause compression lows. After a hypoglycaemic episode, a continuous glucose monitoring system can have a delayed recovery; glucose can normalise before the device detects this rise. If continuous glucose monitoring underestimates blood glucose, this can cause prolonged inappropriate suspension of insulin and a risk of diabetic ketoacidosis. It is crucial that closed-loop systems mitigate this risk by limiting the time of insulin suspension. Additionally, interfering substances, including paracetamol, ascorbic acid, and urea, can cause certain continuous glucose monitors to overestimate blood glucose, potentially leading to the over-delivery of insulin, although many devices contain membranes to filter out select interfering substances.

Like standard insulin pump therapy, closed-loop systems are reliant on a functioning infusion set or cannula from a patch pump. Commercial pumps include pressure alarms to alert users of set failures, but these alarms have low sensitivity for detecting failures. Set failures can lead to marked hyperglycaemia

and diabetic ketoacidosis if not intervened upon. Furthermore, if the system calls for the delivery of insulin, but the insulin is not delivered by the pump due to an error or partial occlusion, the system's estimate of insulin-on-board will be inaccurate. If a problem with a pump occurs and the person takes insulin via a syringe, the closed-loop system will also have an inaccurate estimate of insulin-on-board, which could result in hypoglycaemia. There is a clear need for better infusion sets that are less prone to failure and for standard ways to manage set failures in the setting of closed-loop insulin delivery.

Extended wear infusion sets are eagerly anticipated and a product with a 7-day wear time is now available in Europe [5] and has been approved in the USA. Extended wear infusion sets could reduce scar tissue formation from the subcutaneous cannula, which can limit lifelong use of subcutaneous insulin infusion by decreasing the absorption of insulin and increasing the frequency of occlusions [6].

Closed-loop systems might help to improve glycaemia during exercise, but several user-initiated actions are needed to maximise effectiveness. Future work is required to improve glycaemic outcomes during and following exercise, and the timing and type of exercise need to be carefully considered. For exercise within 2 h of a meal, meal insulin dosing should be reduced (appendix pp 1–2). All current closed-loop systems can set higher glucose targets for exercise, but these targets should be initiated 60–90 min before exercise onset. Although current closed-loop systems deliver only insulin, there might be a benefit to including additional hormones, such as glucagon to reduce hypoglycaemia in response to exercise and pramlintide to reduce postprandial glucose excursions; neither of these hormones are yet approved for use in pumps (appendix pp 1–2).

The burgeoning development of diverse insulin delivery algorithms, additional hormones, peripheral components, and standardised reporting of metrics has opened up new possibilities for closed-loop therapy [7,8]. Although advances in closed-loop therapy could considerably improve health outcomes for people with type 1 diabetes, many cannot afford, or do not have access to, these systems [9]. Addressing disparities in diabetes care will be another challenge to overcome in the years ahead. For those people who do not have access to closed-loop systems or choose not to use them, more sophisticated tools are

needed to improve decision support systems for multiple daily injection therapy [10]. Patients will soon have numerous choices of closed-loop systems and interoperable components. Patients and providers will need to consider which systems are best on the basis of an individual's needs and characteristics. In this 100th year of insulin, we are optimistic for the prospects of closed-loop technologies to achieve further treatment advances for the millions of people worldwide with type 1 diabetes.

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Contact authors

*Leah M Wilson, Peter G Jacobs, Michael C Riddell, Dessi P Zaharieva, Jessica R Castle wilsolea@ohsu.edu Division of Endocrinology, Harold Schnitzer Diabetes Health Center (LMW, JRC) and Artificial Intelligence for Medical Systems Lab, Department of Biomedical Engineering (PGJ), Oregon Health & Science University, Portland, OR 97239, USA; Muscle Health Research Centre, School of Kinesiology and Health Science, York University, Toronto, ON, Canada (MCR); Department of Pediatrics, Stanford University, Stanford, CA, USA (DPZ)

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