Milestone 21

Technology will set you free

Achieving and maintaining normoglycaemia can delay and prevent development of complications associated with type 1 diabetes. This is a significant burden for patients and requires constant monitoring of their blood glucose, and diet and activity levels, as well as precise calculation of the insulin dosages required to lower glucose levels safely to avoid life-threatening hypoglycaemic events.

As early as the fifth century BC, Ayurveda practitioners in India described what we now know as type 1 diabetes using the term Madumeha, which translates as "sweet urine". However, it was not until 1908 that Stanley Benedict developed the first glucose urine test. This test was used for around 50 years until Helen Free introduced Clinistix, which abrogated the need for cumbersome mixing of reagents and heating, and allowed for a simple dipstick measurement of glucose in urine. The Ames Reflectance Meter in the 1970s enabled the measurement of glucose in blood, paving the way for contemporary blood glucose meters. These meters were introduced in the 1980s and have progressively improved in accuracy and are now available as small, handheld devices that require only a very small drop of blood.

"emergence of smart phones and new technologies over the past two decades has culminated in the development of wearable, closed-loop artificial pancreas systems"

Continuous glucose monitors (CGMs), introduced in the late 1990s, rely on a subcutaneous sensor connected to a transmitter to provide a glucose reading every few minutes and are linked to an alarm system to alert the user when glucose levels become dangerously high or low. Advances in insulin delivery systems, including smart pens and pumps, have also accelerated with increased availability of technology. Rapid-acting insulin analogues have also been developed to increase the efficacy of delivery and stability of insulin for use in these devices (Milestone 6).

The emergence of smart phones and new technologies over the past two decades has culminated in the development of wearable, closed-loop artificial pancreas systems designed to monitor glucose and deliver hormones as required, in near real time and with reduced patient input.

The first iterations of artificial pancreas systems, termed hybrid closed-loop systems, pair a CGM device to an insulin pump and rely on an algorithm to calculate required insulin doses. Unlike fully closed-loop systems, hybrid systems perform best if the user informs the algorithm of meals and carbohydrate intake.

In 2014, Russell et al. reported the first outcomes of randomized crossover trials in an outpatient setting using a closed-loop bihormonal delivery system compared with insulin pump therapy. The bihormonal device delivers either insulin or glucagon as needed with only meal announcements required by the user after calibration. Trials in adolescents and adults over the 5-day intervention period demonstrated consistent reductions in mean plasma glucose levels and time in hypoglycaemia compared with the control period.

The following year, Thabit et al. showed increased time of blood levels of glucose within the target range in a randomized crossover study using an insulin-only artificial pancreas, in adults (day and night) and in children and adolescents (overnight), compared with sensor-augmented insulin pump therapy at 12 weeks.

As these devices continue to develop, larger, longer trials under truly free-living conditions have provided assurance of the safety and feasibility of closed-loop systems. Insulin-only devices have also been successfully tested in specific populations, such as pregnant women with type 1 diabetes and hospitalized patients with type 2 diabetes receiving noncritical care, further demonstrating the broad application of these devices.

At present, only a handful of hybrid closed-loop systems have been approved for marketing in Europe and the USA. Large pivotal trials are ongoing with the hope that additional closed-loop systems will soon be available to patients, freeing them of the high daily burden of managing their diabetes.

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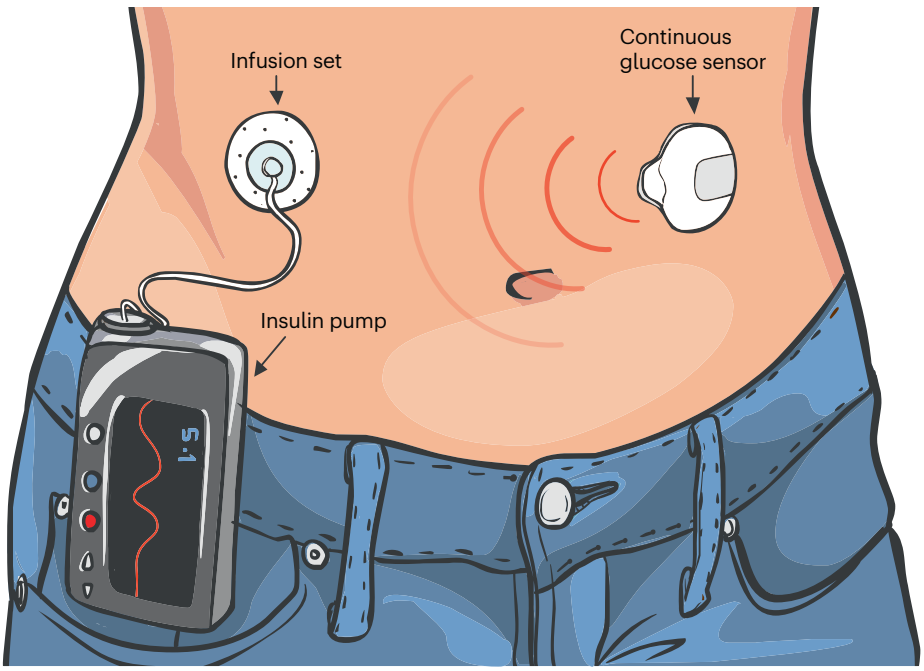

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Milestone studies

Russell, S. J. et al. Outpatient glycemic control with a bionic pancreas in type 1 diabetes. *N. Engl. J. Med.* **371**, 313–325 (2014) | Thabit, H. et al. Home use of an artificial beta cell in type 1 diabetes. *N. Engl. J. Med.* **373**, 2129–2140 (2015)

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