# The artificial pancreas for young people with type 1 diabetes: Status and outlook

Roman Hovorka, Daniela Elleri, Janet M Allen, David B Dunger

**Automated electromechanical closed-loop insulin delivery, also known as the "artificial pancreas", has been a major goal of diabetes treatment research for decades. Foundations date back to the development of blood-based semi-continuous glucose monitoring in the early 1960s, followed by the first commercial hospital-based artificial pancreas in the late 1970s. In the last decade, research into the artificial pancreas has focused on the subcutaneous access route, reflecting advances in interstitial glucose measurement and the increasing use of insulin pumps. The modern artificial pancreas, in the first instance, aims to prevent hypoglycaemia, or to reduce its severity and duration. Following on from promising results under controlled laboratory conditions, clinical studies are now underway to evaluate closed-loop glucose control at home or in home-like settings. This article reviews the current status of closed-loop systems and, in particular, their relevance to paediatric practice.**

**Citation:** Hovarka R, Elleri D, Allen JM, Dunger DB (2012) The artificial pancreas for young people with type 1 diabetes: Status and outlook. *Diabetes Care for Children & Young People* **1**: 49–54

## Article points

1. In recent decades, closed-loop insulin delivery (the "artificial pancreas") has emerged as a promising medical device for the management of type 1 diabetes.
2. The artificial pancreas primarily aims to prevent hypoglycaemia and reduce its severity and duration.
3. The authors conclude that the clinical deployment of the closed-loop system is likely to be a staged process, whereby refinement of the system should not detract from its gradual introduction into the clinical practice.

## Key words

- Artificial pancreas
- Closed-loop system
- Subcutaneous access

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Recent research in the field of therapeutic devices for type 1 diabetes has been geared towards improving glucose monitoring and insulin delivery. Building on these achievements, closed-loop insulin delivery (the "artificial pancreas") is an emerging medical device, which may transform the management of type 1 diabetes (Kowalski, 2009; Hovorka, 2011). The coupling of subcutaneous continuous glucose monitoring (CGM) with insulin pumps in a continually glucose-responsive fashion aims to reduce the risk of hypoglycaemia and improve overall glucose control (Hoeks et al, 2011; Pickup, 2012). This promising approach differs from conventional pump therapy through the use of a control algorithm which directs subcutaneous insulin delivery according to sensor glucose levels every 1–15 minutes. The artificial pancreas may transform the management of type 1 diabetes and improve the quality of life acting as a bridge to the "cure" the condition until alternatives, such as cell-based therapy or immunotherapy, become available. Benefits of the artificial pancreas include low biological risk, innovation and scalability.

## Historical note

The first effort to develop components of the artificial pancreas began with studies on semi-continuous glucose monitoring in 1960. Prototypes of the artificial pancreas adopting intravascular sensing and intravascular delivery in the 1970s then paved the way for the first commercial closed-loop bedside device in 1974, the Biostator (Miles Laboratories Inc, Elkhart, IN, USA). Attempts to miniaturise the Biostator concept followed but given the infection risk and lack of commercially available sensing and delivery devices supporting the intravascular route, the

focus turned in the late 1990s to the subcutaneous route for glucose measurement and insulin delivery, which reflects technological advances in interstitial glucose measurement and the increasing use of insulin pumps.

## Components

Current research is underpinned by commercial CGM devices measuring interstitial glucose as a marker of changes in blood glucose. Although still lacking the accuracy of blood glucose meters, the use of CGM devices improves glucose control and reduces the frequency of hypoglycaemia in adults (Pickup et al, 2011). It is most cost-effective when targeted at people with type 1 diabetes who have continued poor control during intensified insulin therapy and who frequently use CGM (Pickup et al, 2011; Phillip et al, 2012b). The effectiveness of CGM is significantly related to the amount of sensor use, which declines over time and this is of particular concern in adolescents (Phillip et al, 2012a). However, reduced rates of hypoglycaemia were not observed in young people. In toddlers, high parental satisfaction was reported after prolonged CGM without improvements in glycaemic control (Tsalikian et al, 2012).

The established technique of continuous subcutaneous insulin infusion (CSII) uses a portable electromechanical pump to mimic physiological insulin release, infusing insulin at pre-selected rates – normally a slow basal rate with subject-activated boosts at meal times. The use of CSII is growing throughout the world. In the US, approximately 20–25% of people with type 1 diabetes are treated with CSII, while in Europe the application ranges from <1% in countries such as Denmark and 10% in Sweden, the Netherlands and Germany (Selam, 2006).

CGM devices and insulin pumps can be combined to form the artificial pancreas (*Figure 1*). Insulin delivery is then modulated according to real-time interstitial glucose levels, as directed by a control algorithm, rather than at pre-selected rates as with conventional pump therapy.

A control algorithm is a sequence of computer instructions that calculates insulin delivery based on real-time sensor glucose values. Two broad families of control algorithms have been employed clinically: the classical feedback control embodied in the proportional–integral–derivative (PID) controller and the model predictive control. The PID controller continuously adjusts the insulin infusion rate by assessing glucose excursions from three viewpoints: the departure from the target glucose (proportional component), the area under the curve between the actual and target glucose (the integral component) and the change in ambient glucose (derivative component). A model predictive system that will maintain glycaemic control uses a mathematical model linking insulin infusion to glucose excursions. The desired insulin infusion rate is obtained by minimising the difference between the model-predicted glucose concentration and the target glucose trajectory over, for example, a 2–4 hour prediction window corresponding to the duration of action of rapid-acting insulin analogues.

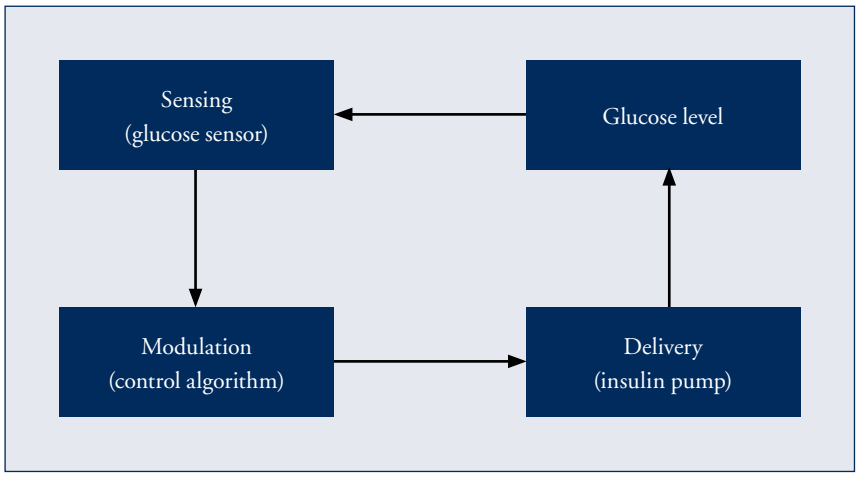


*Figure 1. An illustrative representation of a closed-loop insulin delivery system. Closed-loop systems replicate the physiological feedback normally provided by the beta-cell.*

## Challenges

The development of the artificial pancreas has been hindered by the suboptimal accuracy and reliability of CGM devices, the relatively slow absorption of subcutaneously administered rapid-acting insulin analogues, the lack of adequate control algorithms to account for such imperfection and the variability between and within subjects. These challenges are being gradually overcome (see *Box 1* for the key issues).

Commercially available CGM devices can achieve 15% or lower median relative absolute difference. However, errors of larger magnitude occur, potentially

compromising safety. Minimum performance characteristics for safe closed-loop control are yet to be established. CGM devices present a 5–15 minute time lag between sensor and blood glucose, but this gives little concern for safety, as predictive alarms could be used to warn against impending hypoglycaemia.

It may take 90–120 minutes to reach the maximum extent of blood glucose lowering after administration of the subcutaneous bolus of rapid-acting insulin analogues. This is often under-appreciated. Up to four-fold between-subject variability in rapid-acting insulin pharmacokinetics has been observed, along with as much as 50% within-subject variability on repeated occasions (El-Khatib et al, 2010). A more modest 20–25% within-subject variability has been reported in healthy subjects under controlled conditions. Within-subject variability in insulin requirement includes day-to-day but also hour-to-hour variations owing to circadian and diurnal cycles, the dawn phenomenon, acute illness and stress. Basal insulin requirements are generally lower and age-dependent at 20–40% of the total daily dose in youths and at 50% in adults, which should be reflected in the design of the control algorithm (Davidson et al, 2008; Szypowska et al, 2009).

Large meals challenge closed-loop control. In a "fully closed-loop" mode, insulin is delivered by closed loop without information about meals. Insulin delivery is based on glucose excursions alone (Steil et al, 2006). In a less ambitious configuration using meal announcement and reflecting current practice, closed loop is informed about meal size and, using a Bolus Wizard®-like approach, it may generate advice on prandial insulin bolus (*Figure 2*). Alternatively, the control algorithm may automatically increase insulin delivery based on meal information (Kovatchev et al, 2010). A hybrid approach is characterised by administering a small pre-meal priming bolus between 20% and 75% of the standard bolus or a fixed bolus of 2 units.

Exercise of moderate intensity increases the risk of hypoglycaemia, even during closed-loop glucose control given the rapid decrease in glucose levels and the sustained or even accelerated absorption of

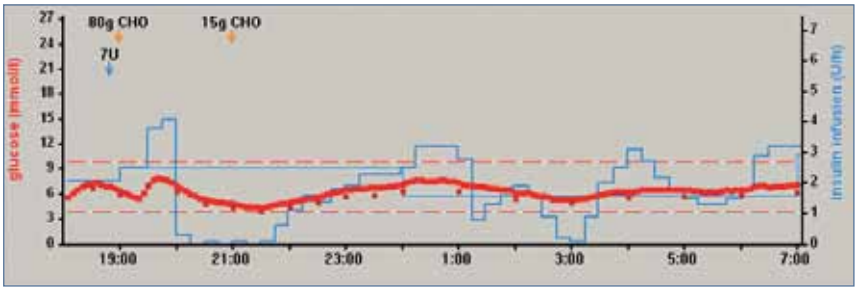


*Figure 2. An example of glucose and insulin profiles observed in a young person with type 1 diabetes (13-year-old boy; duration of diabetes, 5 years; $HbA_{1c}$, 58 mmol/mol [7.5%]; total daily dose, 85 units) during overnight closed-loop insulin delivery. Red thick line denotes continuous glucose readings utilised by a control algorithm to alter between meals and blue thick line denotes insulin delivery every 15 minutes. Dark red squares show the reference plasma glucose concentration used to assess closed-loop performance but not to inform the control algorithm. Thin blue line indicates the pre-programmed basal insulin infusion rates. Vertical orange arrows denote dinner (80 g of carbohydrates) and pre-planned snack (15 g of carbohydrates). Prandial bolus was delivered using Bolus Wizard® (blue vertical arrow). The target glucose range is 3.9–10 mmol/L (red dashed lines). Closed-loop glucose control started at 19.00.*

**Box 1. Key issues of closed-loop systems.**

- Closed-loop systems comprise a continuous glucose sensor, insulin pump and control algorithm.
- Insulin is delivered automatically in a glucose-responsive fashion every 1–15 minutes according to calculations made by the control algorithm.
- Body access through subcutaneous glucose sensing and subcutaneous insulin delivery are most promising.
- Testing under controlled conditions has demonstrated a reduced frequency of hypoglycaemia and increased time in the target glucose range, compared with conventional pump therapy.
- Outpatient studies are planned or underway.
- Introduction of closed-loop delivery into clinical practice may start with simpler approaches, such as hypoglycaemia prevention, progressing to more complex scenarios such as overnight glucose control and control during meals and exercise.

**Page points**

1. More than half of hypoglycaemic events occur during sleep.
2. The overnight closed-loop system could provide a solution to the severe nocturnal hypoglycaemia observed in children and young people, as it is not complicated by meal or physical activity.
3. Closed-loop delivery during waking hours needs to accommodate variability in diet and exercise patterns.

subcutaneously administered insulin. This risk may be during or shortly after exercise, or delayed by several hours. If physical activity takes place after school, the risk of delayed hypoglycaemia will be highest at night time, increasing the incidence of nocturnal hypoglycaemia (Tsalikian et al, 2005).

## Clinical results

Closed-loop systems may be especially interesting in children and young people, where other potentially "curative" treatment options, such as islet cell transplantation, cell-based therapy or immunotherapy, have a relatively high rate of being contraindicated. The use of closed-loop systems in young people and other age groups where poor compliance has a significant impact on the control of diabetes may be a promising treatment option. However, closed-loop systems are limited to those who are able to manage the technology. Clinical results are focused on closed-loop studies in young people.

### Suspended insulin delivery

The simplest form of closed loop involves suspending insulin delivery. This approach has a low regulatory burden as insulin cannot be delivered above the pre-programmed rate but safety assessment needs to demonstrate that excessive hyperglycaemia after suspension is prevented. Medtronic (Watford, Herts) introduced the Paradigm®Veo™ pump, which suspends insulin delivery for up to 2 hours if the hypoglycaemia alarm is not acknowledged. Danne et al (2011) documented a 30–50% reduction in hypoglycaemia frequency with low glucose suspension and a 50% reduction in the duration of hypoglycaemia below 3.9 mmol/L.

Combining five predictive algorithms, Buckingham and colleagues used a more advanced approach to prevent nocturnal hypoglycaemia in children and young people with type 1 diabetes (Buckingham et al, 2010). For the first 14 individuals, hypoglycaemia was induced by gradually increasing the basal insulin infusion rate without the use of pump shut-off algorithms. During the subsequent 26 tests, insulin suspension was initiated at normoglycaemia when sensor glucose was decreasing and two or three algorithms predicted hypoglycaemia. A 35-minute prediction horizon was used with a glucose threshold of 3.9 mmol/L to predict impending hypoglycaemia. The pump shut-off lasted for up to 2 hours. The approach prevented hypoglycaemia (<3.3 mmol/L) on 75% of nights (84% of events) without hyperglycaemia rebound.

Prolonged suspension of insulin delivery can also occur with a closed loop (Cengiz et al, 2009; Elleri et al, 2010). For example, a 90- to 240-minute suspension was considered efficient and led to a peak level of plasma glucose of 11.6 mmol/L, while physiological insulin levels were maintained, indicating that prolonged suspension is a safe and feasible feature of closed-loop systems (Elleri et al, 2010).

### Overnight closed loop

Over 50% of hypoglycaemic events, which are often the most severe, occur during sleep, with most being recorded between 00.00 and 08.00. Overall, 75% of hypoglycaemic seizures in children occur during sleep (Davis et al, 1997). In people with type 1 diabetes under the age of 40 years, 6% of all deaths can be attributed to "dead-in-bed" syndrome, which in many cases may be caused by severe nocturnal hypoglycaemia (Sovik and Thordarson, 1999). As overnight glucose control is not complicated by meals or physical activity, overnight closed-loop systems could provide a solution to this simple yet important clinical problem, which is often of greatest concern to the parents and carers of children and young people with type 1 diabetes.

At Cambridge Biomedical Research Centre, the authors of this article performed randomised studies evaluating overnight closed-loop delivery (Hovorka et al, 2010). Through analysis of the pooled data, the authors reported that there was an increased time when the glucose levels were between 3.9 and 8.0 mmol/L (60% versus 40%) and reduced time when below 3.9 mmol/L (2.1% versus 4.1%), compared with conventional pump therapy. Closed-loop delivery reduced the frequency of plasma glucose levels below 3.3 mmol/L from 7.5% to 0.7%. No events with a plasma glucose concentration lower than 3.0 mmol/L were recorded during closed-loop delivery, compared with nine events during standard treatment. No rescue carbohydrates were administered with the closed loop. Average overnight insulin delivery was similar with the closed loop compared with standard treatment.

### Day-and-night closed loop

Closed-loop delivery during waking hours needs to handle varying diet and exercise patterns. A

group at Yale evaluated the ePID system developed by Medtronic using the PID controller in 17 well-controlled adolescents over 34 hours of closed-loop control (Weinzimer et al, 2008). The fully closed-loop approach without meal announcement was inferior to the meal-announcement approach, accompanied with a small prandial insulin bolus 10–15 minutes before the meal. The overall night glucose levels and associated standard deviations were excellent (6.2±1.5 mmol/L). Three nocturnal hypoglycaemia events (<3.3 mmol/L) were observed. The ePID system was enhanced by predicting the insulin concentration required to prevent insulin stacking and documenting the beneficial effect of manual pre-meal bolus (Weinzimer et al, 2008). Pramlintide co-administration during ePID control delayed the postprandial glucose peak and reduced the magnitude of prandial glucose excursions, particularly after lunch and dinner (Weinzimer et al, 2012). The ePID system with meal dosing was used to achieve normoglycaemia at the onset of diabetes in the hospital setting for which near-normoglycaemia the week after discharge was documented (Buckingham et al, 2012).

Randomised studies at Cambridge using model predictive control over 36 hours in 12 adolescents found a reduction in plasma glucose from 9.0 to 7.2 mmol/L and an increased time in the target range of 3.9–10.0 mmol/L from 55% to 82% with the majority of benefit occurring overnight (Elleri et al, 2011). Nine day-time hypoglycaemia events occurred during closed-loop delivery owing to either an exercise-induced glucose drop, which could not be arrested by stopping basal insulin delivery, or a prandial insulin overdose.

Two versions of a modular model-predictive controller were successfully tested in Virginia, Padova and Montpellier over 22 hours in a randomised crossover design to prevent extreme low and high glucose levels and to optimise control (Breton et al, 2012).

## Other approaches

Glucagon co-administration to prevent hypoglycaemia during closed-loop delivery is being investigated in adults but not yet in young people. The use of intraperitoneal insulin delivery in combination with subcutaneous glucose sensing has also been reported in adults.

*Figure 3. Young person with type 1 diabetes wearing the artificial pancreas – common controller (background) connected to a laptop PC with control algorithm, which communicates wirelessly with the insulin pump (foreground).*

## Outpatient studies

In 2012, results from the first outpatient closed-loop studies were reported. The MD-Logic closed-loop system was compared against sensor-augmented pump therapy in 54 adolescents in diabetes camps in a multinational randomised study design. Preliminary data from one camp are encouraging and indicate a reduction of time when the level of glucose is below 3.5 mmol/L and an increased time in the target range (Phillip et al, 2012a). Remote monitoring identified on average three technical problems per night primarily related to pump connectivity, confirming that the development of reliable wireless communication remains a high priority for outpatient studies.

Another wearable system developed at the University of Virginia underwent feasibility testing in two adults in ambulatory conditions over a single night and the following morning (Renard et al, 2012).

### Page points

1. In 2012, findings from the first outpatient closed-loop studies have emerged.
2. The authors of this article are currently conducting a randomised study evaluating overnight closed-loop in adolescents.
3. The clinical deployment of closed-loop technologies will depend on the appropriate infrastructures being in place, and is likely to be a staged process.

*"The clinical deployment of closed-loop systems is likely to be a staged process, with the aims of reducing the risk of hypoglycaemia and improving glycaemic control, whilst ensuring that safety is preserved."*

At Cambridge, the authors of this article have started a randomised study evaluating overnight closed-loop delivery in adolescents. The FlorenceD system, similar to that shown in *Figure 3*, is used over 3 weeks at home and contrasted against sensor-augmented conventional pump therapy.

## Translation into clinical practice

Success of the artificial pancreas will depend on appropriate infrastructures being in place, such as training resources for users and healthcare professionals, and a support network to manage troubleshooting, data management and possibly remote monitoring.

Factors determining user acceptance of closed-loop technologies will need to be investigated. Experience with CGM devices and insulin pumps suggests that better coping skills, "significant other" involvement, active participation in self-care, and realistic expectations of the benefits of the technology will predict prolonged use and improved health outcomes (Ritholz et al, 2010).

## Conclusion

The clinical deployment of closed-loop systems is likely to be a staged process, with the aims of reducing the risk of hypoglycaemia and improving glycaemic control, whilst ensuring that safety is preserved. Importantly, this phased process of refining closed-loop delivery should not detract from the gradual introduction of the system into the clinical practice. ■

*Roman Hovorka is supported by the Juvenile Diabetes Research Foundation, Diabetes UK, European Commission Framework Programme 7, NIH and Cambridge Biomedical Research Centre.*

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