Technology

The artificial pancreas: One step closer?

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For those with type 1 diabetes and anyone involved in their care, it is hard not to be enthused by the prospect of an artificial pancreas – a closed-loop insulin administration system that delivers insulin by constant, but variable, infusion in response to continuously sensed glucose levels, the rate of delivery determined by a sophisticated algorithm designed to make adjustments on the basis of information from the sensor.

This is one strand of research supported by the Juvenile Diabetes Research Foundation as part of their search for a cure for type 1 diabetes. The group in Cambridge led by Roman Hovorka is one of the centres working on the algorithms and they have published their first portfolio of studies (summarised alongside).

The algorithms have been tested in children with type 1 diabetes, comparing the closed-loop system with conventional insulin-pump delivery for overnight administration, in relation to exercise, and looking at how effectively it works with different meal types. The system is designed to use off-the-shelf components: in this case, the Deltec-Cozmo (Smiths Medical, St Paul, Minneapolis) insulin pump (now withdrawn from the market) with either the Medtronic Guardian® (Northridge California) or Abbott Freestyle Navigator® (Abbott Park, Illinois) real-time continuous glucose monitors. The glucose sensor readings are fed to a computer algorithm every 15 minutes, which advises the insulin infusion rate and, if the rate needs to be adjusted, a nurse makes the alteration.

The results are tantalising rather than groundbreaking. The primary outcomes were time in target range and time spent below 3.9 mmol/L. There is no significant difference in any of the studies in terms of these primary outcomes, except when the data from the overnight and exercise studies are pooled, then significantly more time was spent in target when using the closed-loop system.

> *"An overnight closed-loop system would provide protection from nocturnal hypoglycaemia given the evidence presented and, in particular, could offer a much greater sense of security for children and their families than existing modes of insulin delivery and glucose sensing."*

However, there were no hypoglycaemic episodes (blood glucose <3.0 mmol/L) experienced during closed-loop delivery, compared with nine episodes during standard therapy. Overnight, when insulin delivery is not subject to external influences, time spent in the target range was over twice the duration (79% of the time) with closed-loop compared with insulin-pump delivery. One of the most striking features of the data obtained is the variability of the basal infusion rate overnight, which exposes the deficiencies of current basal insulin therapy, even when delivered by an insulin pump.

The authors admit that a commercial, fully closed-loop system remains many years away, but partial closed-loop systems could be available very soon. An overnight system, for example, would provide protection from nocturnal hypoglycaemia given the evidence presented and, in particular, could offer a much greater sense of security for children and their families than existing modes of insulin delivery and glucose sensing. Potential parental satisfaction with such a system is confirmed by the related paper by Elleri et al (2010; summarised overleaf).

LANCET

Closed-loop algorithm performs well overnight

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓✓

1 An algorithm that calculates the appropriate dose of insulin based on continuous glucose monitoring (CGM) measurements was tested overnight in 19 children with type 1 diabetes.

2 Three cross-over studies were undertaken: standard continuous subcutaneous insulin infusion (CSII) compared with closed-loop insulin delivery using the algorithm (n=13; APCam01); closed-loop insulin delivery after slowly and rapidly-absorbed meals (n=7; APCam02); and closed-loop insulin delivery compared with standard treatment after exercise (n=10; APCam03).

3 During closed-loop nights, glucose measurements were fed into the algorithm every 15 minutes and a nurse adjusted the insulin pump. Participants applied their standard insulin pump settings during the control nights.

4 The primary outcome was the time that glucose was within the target range (3.91–8.00 mmol/L).

5 The primary outcome was not significantly different across all treatment groups. The time participants of the APCam01 study spent within the target range improved from a median of 39% to 52% with the closed-loop system (P=0.06).

6 A secondary analysis, pooling data from all three studies revealed that the amount of time spent within the target range was 60% with closed-loop insulin delivery and 40% during standard treatment (P=0.002), increasing to 75% after midnight when the closed-loop system became fully effective.

7 The authors concluded that the closed-loop system reduced the risk of nocturnal hypoglycaemia in children with type 1 diabetes.

Hovorka R, Allen JM, Elleri D et al (2010) Manual closed-loop insulin delivery in children and adolescents with type 1 diabetes: a phase 2 randomised crossover trial. *Lancet* **375**: 743–51

DIABETES TECHNOLOGY & THERAPEUTICS

Timing of pre-meal insulin dose

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓

1 The authors of this study aimed to establish the most effective timing of a prandial insulin dose in children with type 1 diabetes treated with an insulin pump.

2 Participants were 30 children (17 boys) with a mean age of 15.2±3.9 years, mean diabetes duration of 8.07±4.1 years and mean insulin requirement of 0.77±0.21 U/kg/day.

3 The study was conducted in hospital and all children stayed in hospital for 3 days. Each test meal was individually tailored to meet the needs of the child and the same test meal was consumed by the child at lunchtime for three consecutive days.

4 Prandial insulin doses were given either 15 minutes before, immediately before, or immediately after consumption of the meal.

5 Blood glucose levels were taken 15 minutes before the meal, immediately before and 30, 60, 90, 120 and 180 minutes after the meal.

6 None of the participants experienced severe hypoglycaemia. Blood glucose readings were not significantly different during the 3 days.

7 Glucose levels were lower (but not significantly) 3 hours after the meal when bolus doses had been administered 15 minutes or immediately before the meal rather than after the meal.

8 The standard deviation of the area under the curve (in mg/min) was lowest with the bolus given 15 minutes before the meal. This supports administration of a bolus dose before eating.

Scaramuzza AE, Iafusco D, Santoro L et al (2010) Timing of bolus in children with type 1 diabetes using continuous subcutaneous insulin infusion (TiBoDi Study). *Diabetes Technol Ther* **12**: 149–52

JOURNAL OF DIABETES SCIENCE AND TECHNOLOGY

Veo™ versus REAL-Time calibration algorithms

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

1 A total of 72 adults took part in this multicentre study evaluating the efficacy of the Paradigm® REAL-Time (PRT; Medtronic Diabetes, Northridge, CA) sensor-augmented insulin pump system compared with that of the Paradigm® Veo™ insulin pump (PV; Medtronic Diabetes).

2 A total of 7193 sensor downloads and 90 472 paired data points (sensor and meter values) were analysed.

3 The PV calibration algorithm increase hypoglycaemia sensitivity to 82.3% compared with 54.9% in the PRT, but hypoglycaemia sensitivity decreased to 81.7% in the PV compared with 86% in the PRT.

4 The PV calibration algorithm improves hypoglycaemia detection compared with the PRT.

Keenan DB, Cartaya R, Mastrototaro JJ (2010) Accuracy of a new real-time continuous glucose monitoring algorithm. *J Diabetes Sci Technol* **4**: 111–8

JOURNAL OF DIABETES SCIENCE AND TECHNOLOGY

Siphon effect in tubing affects rate of insulin delivery

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

1 The authors of this study aimed to quantify hydrostatic effects on the delivery of bolus and basal insulin doses with an insulin pump.

2 Insulin pumps from three manufacturers were tested and the fluid level change was measured using an inline graduated glass pipette when the pipette was moved relative to the pump, and when both were level.

3 There were large differences in basal insulin delivery in insulin pumps with 80–100 cm tubing, ranging from 74.5% of the expected delivery when the pump was below the pipette to 123.3% when the pump was above the pipette.

4 A siphon effect in the tubing of conventional insulin pumps may affect the accuracy of insulin delivery.

Zisser HC, Bevier W, Dassau E, Jovanovic L (2010) Siphon effects on continuous subcutaneous insulin infusion pump delivery performance. *J Diabetes Sci Technol* **4**: 98–103

DIABETES TECHNOLOGY & THERAPEUTICS

Parents welcome closed-loop concept

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓✓

1 Parental attitudes towards closed-loop insulin delivery (CLID) in children with type 1 diabetes were investigated.

2 A total of 19 parents anonymously completed a questionnaire after a focus meeting where the concept of CLID was explained and results of studies at Cambridge were presented.

3 The responses revealed that parents' main concerns related to long-term complications (84%) and hypoglycaemia (16%).

4 Parents found glycaemia most difficult to manage at night time (56%), which worried most parents (71%) particularly because of fear of hypoglycaemia (33%).

5 All welcomed the development of CLID to manage diabetes. Most (90%) parents were not worried about a computer controlling their child's overnight insulin delivery.

6 The authors found that the concept of CLID was accepted by this group of parents and a commercially available system will be an important goal.

Elleri D, Acerini CL, Allen JM et al (2010) Parental attitudes towards overnight closed-loop glucose control in children with type 1 diabetes. *Diabetes Technol Ther* **12**: 35–9

"*A siphon effect in the tubing of conventional insulin pumps may affect the accuracy of insulin delivery.*"