DIABETES CARE

Bionic pancreas achieves excellent glycaemic control

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

1 A longstanding goal of T1D treatment has been to develop a fully or semi-automated device that achieves glycaemic goals, minimises hypoglycaemia and lessens the burden on the individual with type T1D.

2 The authors previously reported that bihormonal therapy with subcutaneous insulin and glucagon directed by a computer algorithm using frequently sampled plasma glucose (PG) was safe and efficacious in sedentary participants over 27 hours; they also compared the effectiveness of three continuous glucose monitors (CGMs).

3 In this study the authors tested whether safe and effective glycaemia could be achieved using a bihormonal bionic endocrine pancreas driven by a CGM for more than 2 days and including six carbohydrate meals (mean carbohydrate consumption 78±12 g per meal) and exercise challenges (30 minutes on a stationary bicycle, regardless of PG).

4 Six adults with T1D participated in two 51-hour studies; blood glucose was managed with a bionic endocrine pancreas, which controlled delivery of insulin and glucagon with insulin pumps under closed-loop control.

5 The overall mean PG was 158 mg/dL – 68% of PG values were within the range 70–180 mg/dL; hypoglycaemia (<70 mg/dL) was rare.

6 The authors concluded that, despite high-carbohydrate meals and exercise, the bihormonal bionic endocrine pancreas achieved excellent glycaemic control for over 2 days' continuous use with minimal hypoglycaemia.

Russell SJ, El-Khatib FH, Nathan DM et al (2012) Blood glucose control in type 1 diabetes with a bi-hormonal bionic endocrine pancreas. *Diabetes Care*. doi: 10.2337/dc12-0071

Moving towards the goal of a bionic pancreas

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Many individuals with T1D will ask about pump therapy when they are struggling to live with diabetes on a day-to-day basis. Clinicians will recognise this familiar situation; a person with T1D has been running an HbA_{1c} of around 9.5% (80 mmol/mol) for some time — he or she has learnt about carbohydrate counting, has received advice on optimising insulin therapy, and has had few hypoglycaemic episodes, but, despite this, has not been able to improve his or her overall glucose control. The talk then turns to insulin pumps. It becomes clear that what the individual is looking for is something that will provide a break from diabetes – something that will remove the need for constant attention to detail when trying to balance insulin dose, carbohydrate counting and the influence of other factors such as physical activity.

Unfortunately, at this time, the available technology cannot do this; it would seem that this remains a distant goal, not yet in sight but perhaps just over the horizon. The optimist might say that this may perhaps be sooner than we think. The paper by Russell and colleagues (2012; summarised alongside) together with the paper by O'Grady et al (2012; summarised below) demonstrate the current effort to develop an artificial pancreas – something that could control blood glucose with no conscious effort on the part of the individual.

The key components of the artificial pancreas are a device to deliver insulin together with a device to sense glucose and a control algorithm to link the two. The islets of Langerhans combine these functions with the ability to sense and respond to changing blood glucose levels; they contain cells that produce not only insulin but also glucagon. Russell and colleagues have tried to mimic this; they report a system that combines continuous glucose monitoring with a simultaneous infusion of both insulin and glucagon delivered via a commercially available insulin pump.

Subjects were closely supervised during the study period and the system required manual assistance with the mealtime bolus. There were a number of technical failures and episodes of minor hypoglycaemia during the 12 days of the study; but, despite this, the researchers felt that the system was capable of achieving reasonable glucose control.

This paper not only represents proof of concept but joins the growing literature describing closed-loop systems. The remaining major concern is the safety of these systems. It seems likely that the first clinical use will be the introduction of overnight closed-loop systems to manage nocturnal hypoglycaemia, but even this would be a major step forward. Perhaps the artificial pancreas is not as far away as we might think…

DIABETES CARE

PGCS achieves nocturnal control

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

1 The authors sought to determine the efficacy and safety of a fully automated, portable, closed-loop artificial pancreas system – the Medtronic Portable Glucose Control System (PGCS).

2 Eight young people with T1D used to insulin pump therapy each attended two nights in the clinic for PGCS (closed-loop) monitoring; the PGCS had fault detection capabilities to ensure patient safety.

3 The PGCS maintained mean overnight plasma glucose levels of 6.4±1.7 mmol/L; the proportion of time with venous plasma glucose <3.9 mmol/L, 3.9–8.0 mmol/L and >8.0 mmol/L was 7%, 78% and 15%, respectively.

4 Time in target range (between 3.9 and 8.0 mmol/L) was greater during closed-loop than open-loop operation (84.5% versus 46.7%, respectively; $P<0.0001$).

5 The authors concluded that the PGCS safely and effectively achieves overnight glucose control in young people with T1D.

O'Grady MJ, Retterath AJ, Keenan DB et al (2012) The use of an automated, portable, glucose control system for overnight glucose control in adolescents and young adults with type 1 diabetes. *Diabetes Care* **35**: 2182–7

"Data do not support the hypothesis that severe hypoglycaemia increases the risk of cardiovascular disease in individuals with T1D."

DIABETES CARE

CVD risk not increased by severe hypoglycaemia

Readability	✓
Applicability to practice	✓
WOW! factor	✓

1 Intensive glucose control in T1D can increase the risk of severe hypoglycaemia, which some studies have suggested may increase the risk of cardiovascular disease (CVD).

2 The authors examined the relationship between severe hypoglycaemia and CVD incidence in a 7-year, prospective cohort study of 2181 individuals with T1D recruited from the EURODIAB Prospective Complications Study.

3 Episodes of severe hypoglycaemia were self-reported by questionnaire at baseline and follow-up, and incidence of fatal and non-fatal CVD were determined at 6–8 years' follow-up after the baseline examination.

4 During a median follow-up of 7.3 years, 176 individuals had incident CVD (fatal or non-fatal): 114 reported none (7.6%; 12 fatal, 102 non-fatal), 33 reported one or two (7.9%; 3 fatal, 30 non-fatal), and 29 reported three or more severe hypoglycaemic episodes (10.8%; 29 non-fatal).

5 In those reporting (9.0%) and not reporting (7.5%) severe hypoglycaemia at baseline and at follow-up, the proportion of individuals who had fatal or non-fatal CVD events was comparable (P=0.22) .

6 Logistic regression analysis showed that severe hypoglycaemia at baseline was not associated with incidence of CVD (adjusted odds ratio [95% confidence interval]: one or two episodes, 0.87 [0.55–1.37]; three or more episodes, 1.09 [0.68–1.75]).

7 The authors concluded that the data do not support the hypothesis that severe hypoglycaemia increases the risk of CVD in individuals with T1D.

Gruden G, Barutta F, Chaturvedi N et al (2012) Severe hypoglycaemia and cardiovascular disease incidence in type 1 diabetes. *Diabetes Care* **35**: 1598–604

DIABETES

Life expectancy improved over time for people with T1D

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

1 The authors set out to assess the impact of T1D on life expectancy in the US, which, to date, has not been determined.

2 The Pittsburgh Epidemiology of Diabetes and Complications study is a prospective cohort of childhood-onset T1D diagnosed between 1950 and 1980; this enabled the authors to examine mortality and life expectancy changes over time in a US cohort with >30 years' follow-up.

3 Improvements in life expectancy were compared between two sub-cohorts: 390 individuals were diagnosed with childhood-onset T1D between 1950 and 1964, and 543 individuals were diagnosed between 1965 and 1980.

4 The difference in observed survival between the sub-cohorts was assessed using Kaplan–Meier curves and the log-rank statistic; abridged life tables were constructed to calculate life expectancy.

5 In total, 237 (60.8%) people died in the 1950–1964 sub-cohort and 88 (16.2%) died in the 1965–1980 sub-cohort.

6 From the Kaplan–Meier curves, crude survival was greater in the 1965–1980 sub-cohort (log-rank test, P<0.0001) than in the earlier group.

7 The life expectancy at birth for those diagnosed in 1965–1980 was 68.8 years (95% confidence interval [CI], 64.7–72.8), which is about 15 years greater than the life expectancy for those diagnosed between 1950 and 1964 (53.4 years, 95% CI, 50.8–56.0; P<0.0001).

8 The authors concluded that these life expectancy estimates could influence US health insurance company premiums.

Miller RG, Secrest AM, Sharma RV et al (2012) Improvements in the life expectancy of type 1 diabetes: The Pittsburgh Epidemiology of Diabetes Complications Study cohort. *Diabetes* **61**: 2987–92

ENDOCRINE PRACTICE

High burden of ambulance call-out for hypoglycaemia in T1D

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

1 The study objectives were to determine the population burden of ambulance call-out for hypoglycaemia, and long-term outcomes in individuals with T1D on different insulin regimens.

2 All calls to ambulance emergency services concerning hypoglycaemia for T1D in Olmsted County, Minnesota, USA, between 1 January 2003 and 31 December 2009 were retrieved, and medical records reviewed.

3 During the study period, 531 ambulance calls were made by 208 individuals with T1D (age 47±13 years; 54% male) for hypoglycaemia.

4 Of the callers, 137 (66%) were on multiple daily insulin (MDI) injections, 50 (24%) on continuous subcutaneous insulin infusion, 15 (7%) on simple insulin (SI), 4 (2%) on metformin in conjunction with MDI injections and 2 (1%) off insulin after a pancreas transplant; due to small sample sizes, the latter two groups were excluded from analysis.

5 Repeated calls to the emergency services, ambulance transportation and hospitalisation was 32%, 51% and 19%, respectively, and did not differ between the treatment groups.

6 Treatment type significantly influenced mortality, which was higher in the SI group than in the MDI injection group (P=0.03). Other influencing factors included increasing age (P<0.0001) and requiring ambulance transportation (P=0.04).

7 The authors concluded that burden of hypoglycaemia in T1D on ambulance call-out was high.

Parsaik AK, Carter RE, Myers LA et al (2012) Population-based study of hypoglycaemia in type 1 diabetes requiring emergency medical services. *Endocr Pract* 11 Jul [Epub ahead of print]

DIABETES CARE

IDegAsp regimen offers glycaemic control with fewer daily injections

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

1 Insulin degludec and insulin aspart coformulation (IDegAsp) provides the total daily basal insulin requirement and the bolus insulin requirement for one main meal; insulin aspart (IAsp) is used at other meals.

2 The authors set out to confirm the efficacy and tolerability of once-daily administered IDegAsp (taken at a main meal) plus IAsp taken at other meals, and to compare it with a standard basal-bolus regimen using insulin detemir (IDet) and IAsp.

3 In total, 548 adults with T1D were randomised 2:1 to IDegAsp (given with a meal; *n*=366) or IDet once daily (given in the evening; *n*=182), both in combination with IAsp (at other mealtimes), in a 26-week, multinational, parallel-group, treat-to-target trial.

4 HbA_{1c} improved by 0.75% (8.2 mmol/mol) with IDegAsp and 0.70% (7.65 mmol/mol) with IDet to 7.6% (60 mmol/mol) in both groups; non-inferiority of IDegAsp to IDet was confirmed.

5 There was no statistically significant difference in the rates of hypoglycaemia (severe or overall confirmed) between treatment regimens, although nocturnal hypoglycaemia was 37% lower with IDegAsp than IDet (3.71 versus 5.72 episodes/person-year, $P<0.05$). Total insulin was 13% lower in the IDegAsp group ($P<0.0001$).

6 The authors concluded that, compared with the IDet and IAsp regimen, the IDegAsp regimen with bolus IAsp improved glycaemic control comparatively with fewer injections and a reduced risk of nocturnal hypoglycaemia.

Hirsch IB, Bode B, Courreges JP et al (2012) Insulin degludec/insulin aspart administered once daily at any meal, with insulin aspart at other meals, versus a standard basal-bolus regimen in patients with type 1 diabetes. *Diabetes Care* **35**: 2174–81

DIABETIC MEDICINE

Moderate-to-vigorous physical activity achieves better glycaemia

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

1 It is essential to improve glycaemic control in childhood-onset diabetes; however, there is uncertainty about the association between physical activity, fitness and HbA_{1c} levels in young people with T1D.

2 The authors assessed physical activity and fitness levels of 60 young people with T1D (aged 8–16 years) and compared these with a control group of 37 siblings of the same age group without diabetes.

3 Measurements of weight, height, waist circumference, BMI, blood pressure (BP) and any insulin regimen information were recorded. Pubertal status was also assessed.

4 Participants wore an accelerometer for 7 days to assess physical activity levels; data recorded were used to calculate light and moderate-to-vigorous intensity activity. Physical fitness was determined by a multistage submaximal bicycle ergometer test. HbA_{1c} was also measured.

5 Both groups had similar measures of body composition, BP, physical activity and fitness.

6 Moderate-to-vigorous physical activity was associated with better glycaemic control, accounting for 30–37% (coefficient of determinations [R^2]=0.295–0.374) of the variance for HbA_{1c}. Physical fitness was not associated with HbA_{1c}.

7 The authors concluded that strategies to increase moderate-to-vigorous physical activity may prove an effective method to improve glycaemic control in young people with T1D.

Cuence-García M, Jago R, Shield JP et al (2012) How does physical activity and fitness influence glycaemic control in young people with type 1 diabetes? *Diabet Med* **29**: e369–76

DIABETES CARE

Walking improves postprandial glycaemia

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

1 The effect of low-intensity physical activity, such as walking, on glucose variability in healthy people and people with T1D has not been studied.

2 In total, 12 healthy controls (aged 37.7±13.7 years; five men) and 12 individuals with T1D (aged 37.4±14.2 years; five men) were studied for 88 hours; the authors hypothesised that glucose excursions would be blunted in individuals with T1D undergoing low-intensity physical activity.

3 Participants spent 3 days and 4 nights in the clinical research unit; throughout the study each wore a continuous glucose sensor (to monitor interstitial fluid glucose concentrations) and a physical activity-monitoring system suit equipped with accelerometers.

4 In random order, one meal per day was followed by inactivity and the other meals were followed by walking at 1.9 kmph for 33.5 minutes. Glucose and physical activity data for a total of 216 meals were analysed from 30 minutes before the meal to 270 minutes postprandially.

5 In the control group, the incremental glucose area under the curve was 4.5 mmol/L/270 minutes for meals followed by physical activity and 9.6 mmol/L/270 minutes ($P=0.022$) for meals followed by inactivity. In the T1D group these results were 7.5 mmol/L/270 minutes and 18.4 mmol/L/270 minutes, respectively ($P<0.001$).

6 The authors concluded that low-grade physical activity, such as walking, significantly improved postprandial glycaemia.

Manohar C, Levine JA, Nandy DK et al (2012) The effect of walking on postprandial glycaemic excursion in patients with type 1 diabetes and healthy people. *Diabetes Care* 8 Aug [Epub ahead of print]

> *"Strategies to increase moderate-to-vigorous physical activity may prove an effective method to improve glycaemic control in young people with T1D."*