Management of type 1 diabetes

A focus on glucagon

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The reality of glucose sensor/insulin pump closed-loop therapy now feels close. There have been two parallel approaches; one system uses current insulin pump technology, the other uses a combined insulin and glucagon pump, with glucagon being infused as interstitial glucose falls. The paper by El-Khatib and colleagues (summarised alongside) is the latest publication from the group in Boston describing their experience of what they call "the bionic pancreas". They describe a short-term study of individuals using a dual infusion of insulin and glucagon, and show that the system results in improved glucose control and, most importantly, is safe. Having said that, the system using just insulin has shown similar results and we do not have a head-to-head comparison. The question now is whether glucagon, which has some disadvantages, provides significant additional benefits in free-living individuals using a closed-loop system? We do not know the answer.

One of the interesting debates that has emerged is the wider role of glucagon in the management of type 1 diabetes. In normal physiology, glucagon plays an important role in responding to falling blood glucose, with glucagon stimulating glycogen release from the liver. In type 1 diabetes, this glucagon response is lost, and individuals with the condition need to take additional carbohydrate to manage falling glucose, which can result in large fluctuations in blood glucose. Potentially, glucagon has a role as a day-to-day treatment alongside insulin for the management of a much larger group of people with type 1 diabetes.

Because there is no stable formulation of glucagon, it has, until now, been seen as a niche drug in the management of hypoglycaemic emergencies. Because it has been seen as a medication with limited use, there has been no incentive for the pharmaceutical companies to develop a more usable formulation. Now, however, there is renewed interest in developing a formulation of glucagon that could be used in the same sort of delivery devices as insulin.

Diabetes Care

Is excess BMI in childhood a T1D risk factor?

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓✓

1 These authors studied 1117 subjects (aged between 2 and 18 years) in the TrialNet Pathway to Prevention cohort between 2004 and 2014, to determine the effect of elevated BMI over time on T1D progression in youth.

2 Cumulative excess BMI (ceBMI) was used to measure persistent BMI elevation over the 85th percentile for age- and gender-adjusted BMI. This is the first study to apply ceBMI methodology to T1D.

3 The risk of T1D progression was greater in individuals with high ceBMI but occurred at lower ceBMI values in those <12 years old. Males overall had a higher ceBMI diabetes risk threshold than females, suggesting an increased sensitivity to the effect of elevated BMI in female subjects.

4 The authors conclude that elevated BMI is associated with increased risk of progression to T1D in an at-risk paediatric population. However, the effect varies by gender and age.

Ferrara CT, Geyer SM, Liu Y et al (2017) Excess BMI in childhood: a modifiable risk factor for type 1 diabetes development? *Diabetes Care* **40**: 698–701

Lancet

Bionic pancreas vs insulin pump therapy in the home setting

Readability	✓✓✓
Applicability to practice	✓✓
WOW! Factor	✓✓✓✓✓

1 This randomised, crossover study evaluated the safety and effectiveness in adults with T1D of an automated glycaemic control system using both insulin and glucagon in an unrestricted home-use setting. The system was initialised based solely on the participant's body mass.

2 Participants completed two 11-day study periods in a random order. During the intervention period, individuals used the bihormonal bionic pancreas. In the comparator period, participants used their own insulin pump and, if they used one, continuous glucose monitor (CGM).

3 The bihormonal bionic pancreas consisted of an Apple iPhone 4S connected to a Dexcom G4 Platinum CGM. Administration of the hormones was controlled by an app on the iPhone.

4 For study completers (n=39), mean glucose concentration was 7.8 mmol/L during the intervention period compared with 9.0 mmol/L in the comparator period (difference 1.1 mmol/L; P<0.0001).

5 Mean time with glucose concentration <3.3 mmol/L was 0.6% with the bionic pancreas and 1.9% during the comparison (difference 1.3%; P<0.0001). The bionic pancreas also reduced symptomatic hypoglycaemic events by 0.31 events/day, although nausea increased.

6 The authors conclude that their bionic pancreas achieved superior glycaemic regulation without the need for carbohydrate counting.

El-Khatib FH, Balliro C, Hillard MA et al (2016) Home use of a bihormonal bionic pancreas versus insulin pump therapy in adults with type 1 diabetes: a multicentre randomised crossover trial. *Lancet* **389**: 369–80

Diabetes Care

Insulin glargine in adults with T1D

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! Factor	✓✓✓

1 Despite advances in basal insulin therapy, people with T1D still experience fluctuating glucose levels as well as glucose excursions.

2 This two-period crossover study compared glucose control in adults with T1D receiving once-daily insulin glargine 300 units/mL or 100 units/mL in the morning or evening, in combination with mealtime insulin, over two successive 8-week treatment periods.

3 Continuous glucose monitoring was used to compare glucose control, safety and tolerability between glargine 300 units/mL (n=30) and 100 units/mL (n=29) when administered at the same times each day.

4 The percentage of time spent within the target glucose range of 4.4–7.8 mmol/L during the last 2 weeks of treatment was comparable between the two groups.

5 Glucose levels increased significantly less during the last 4 hours of the 24-hour injection interval for glargine 300 units/mL compared with 100 units/mL (least mean square difference, −0.8 mmol/L; P=0.02).

6 Glycaemic excursions were lower, irrespective of morning or evening injection, in the glargine 300 units/mL group. The rate of hypoglycaemia was also lower in this group.

7 These results imply that insulin glargine 300 units/mL should improve the flexibility of the injection schedule (morning or evening) without compromising glycaemic control.

Bergenstal RM, Bailey TS, Rodbard D et al (2017) Comparison of insulin glargine 300 units/mL and 100 units/mL in adults with type 1 diabetes: continuous glucose monitoring profiles and variability using morning or evening injections. *Diabetes Care* **40**: 554–60

Diabetes Technol Ther

Reducing hypoglycaemia using SAP and Smartguard

Readability	✓✓✓
Applicability to practice	✓✓
WOW! Factor	✓✓

1 This study investigated whether a sensor-augmented insulin pump (SAP) using Dexcom's MiniMed 640G system with SmartGuard technology offered additional protection beyond conventional SAP therapy for paediatric users.

2 SmartGuard allows insulin delivery to be suspended automatically based on prediction of low blood glucose levels.

3 Participants (n=24) used an SAP without suspension features for 2 weeks (phase 1). SAP therapy plus SmartGuard was then used for 6 weeks (phase 2). The suspension threshold for hypoglycaemia was 3.9 mmol/L.

4 In phase 2, the number of instances in which glucose levels were <3.9 mmol/L was reduced from 1.02 ± 0.52 to 0.72 ± 0.36 per day (P=0.03). In addition, the area under the curve <3.9 mmol/L was halved (P=0.03).

5 The reduction in hypoglycaemia in phase 2 was not associated with a significant change in mean glucose concentration or HbA_{1c}.

6 Compared to SmartGuard suspensions that were resumed automatically, manual resumptions followed by carbohydrate intake resulted in significantly higher glucose levels after 1 hour.

7 The best results were obtained when the user did not interfere with pump operation. Users should not be nervous about suspensions during normoglycaemia as the device uses a predictive algorithm.

Biester T et al (2017) "Let the algorithm do the work": Reduction of hypoglycemia using sensor-augmented pump therapy with predictive insulin suspension (SmartGuard) in pediatric type 1 diabetes patients. *Diabetes Technol Ther* **19**: 173–82

Diabetes Obes Metab

Degludec 200 units/mL vs glargine 300 units/mL

Readability	✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓

1 This double-blind, crossover study compared the day-to-day and within-day variability in pharmacodynamic properties of insulin degludec 200 units/mL and insulin glargine 300 units/mL in adults with T1D.

2 Participants were randomised to 0.4 units/kg of degludec or glargine once daily for two treatment periods of 12 days each. Variables were assessed at steady state from the glucose infusion rate profiles of three 24-hour euglycaemic clamps at days 6, 9 and 12 during each treatment period.

3 In total, 57 individuals completed both treatment periods. The potency of glargine was 30% lower than that of degludec (P<0.0001). The distribution of the glucose-lowering effect was stable across the 6-hour intervals for degludec, while the effects of glargine were greater in the first and last intervals.

4 Within-day variability was 37% lower with degludec than with glargine (P<0.0001). Day-to-day variability with degludec was about four times lower than with glargine (P<0.0001). Day-to-day variability assessed in 2-hour intervals over 24 hours was consistently low with degludec, but steadily increased with glargine to a maximum at 10–12 and 12–14 hours.

5 The authors conclude that people treated with degludec 200 units/mL might achieve lower glycaemic targets with a reduced risk of hypoglycaemia compared to glargine 300 units/mL.

Heise T, Nørskov M, Nosek L et al (2017) Insulin degludec: Lower day-to-day and within-day variability in pharmacodynamic response compared with insulin glargine 300 U/mL in type 1 diabetes. *Diabetes Obes Metab* **19**:1032–39

"Potentially, glucagon has a role as a day-to-day treatment alongside insulin for the management of a much larger group of people with type 1 diabetes."