Management of type 1 diabetes

New glucagon delivery routes for the treatment of hypoglycaemia

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Administering intramuscular glucagon to a friend or partner experiencing a severe hypoglycaemic episode cannot be much fun. Often, the first aider has never had to do it before or it was so long ago that they have forgotten. People having a severe hypo are often not very cooperative, and plunging a needle into a moving thigh may be difficult. Furthermore, following correction of the hypoglycaemia, there are the after-effects: nausea, vomiting and rebound hyperglycaemia. Altogether, therefore, glucagon treatment of insulin-induced hypoglycaemia has its limitations.

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The papers by Rickels et al and Ranjan et al (summarised alongside and on the facing page) offer alternative and potentially more effective uses of glucagon. Although the glucose response to intranasal glucagon is slower than that of the intramuscular route, the former may be simpler and quicker to deliver. Unfortunately, the gastrointestinal side effects are similar between the two delivery routes, occurring in about one third of participants.

Judging by the paper by Ranjan and colleagues, however, these effects appear to be dose-related and, when small doses are given subcutaneously in response to mild hypoglycamia, rebound hyperglycaemia can be limited. For the majority of insulin-treated people, there will be no practical value of using subcutaneous glucagon in place of oral glucose for mild degrees of hypoglycaemia, but for people on closed-loop systems the former may prove to be a valuable non-calorific addition to this emerging technology. Watch this space! ■

Diabet Med

Aerobic fitness is associated with exercise-induced hypoglycaemia

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

1 This study was conducted to assess the impact of physical fitness on hypoglycaemia risk during exercise in people with T1D.

2 A total of 44 people with T1D (34 adults, 10 adolescents) who were treated with insulin pump therapy underwent a standardised exercise session. Fitness (maximum oxygen intake) was classified according to established norms for age and gender as either good (≥25th percentile) or poor (<25th percentile).

3 Hypoglycaemia (plasma glucose <4 mmol/L) occurred in 17 of 23 fit participants (74.%) vs 8 of 21 unfit participants (38%; P=0.02).

4 Despite similar pre-exercise levels, plasma glucose fell to a greater extent in the fit group (–4.6 mmol/L vs –2.1 mmol/L; P=0.01).

5 The authors conclude that people with T1D who have good cardiorespiratory fitness are more prone to hypoglycaemia during exercise. This may be due to better insulin sensitivity and the fact that they tend to exercise at greater work thresholds.

Al Khalifah RA, Suppère C, Haidar A et al (2016) Association of aerobic fitness level with exercise-induced hypoglycaemia in type 1 diabetes. *Diabet Med* 16 Jan [Epub ahead of print]

Diabetes Care

Efficacy and safety of intranasal glucagon to treat hypoglycaemia

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

1 In this multicentre, crossover, randomised controlled trial, an intranasal, powdered preparation of glucagon was compared with an intramuscular glucagon injection to treat hypoglycaemia.

2 In a clinic visit, participants had hypoglycaemia induced with a controlled excessive dose of insulin and were randomised to receive the intranasal or intramuscular glucagon. In a subsequent visit they underwent the same procedure but with the other agent.

3 Success criteria (restoration of plasma glucose to ≥3.9 mmol/L or to ≥1.1 mmol/L above the glucose nadir) were met in 98.7% of the intranasal arm (74 of 75 participants) and 100% of the intramuscular arm.

4 Restoration to normoglycaemia was 3 minutes slower in the intranasal group (mean time to success, 16 vs 13 minutes; P<0.001).

5 In the safety analyses, head or facial discomfort was reported by 25% of intranasal and 9% of intramuscular recipients, and nausea (with or without vomiting) occurred in 36% and 38%, respectively.

6 The authors conclude that intranasal glucagon is effective and safe for the treatment of insulin-induced hypoglycaemia. This route of administration should be easier in real-world settings, as the powdered dose does not require preparation and the delivery method is simpler than an intramuscular injection.

Rickels MR, Ruedy KJ, Foster NC et al (2016) Intranasal glucagon for treatment of insulin-induced hypoglycemia in adults with type 1 diabetes: a randomized crossover noninferiority study. *Diabetes Care* **39**: 264–70

"The authors conclude that intranasal glucagon is effective and safe for the treatment of insulin-induced hypoglycaemia. This route of administration should be easier in real-world settings, as the powdered dose does not require preparation and the delivery method is simpler than an intramuscular injection."

Diabetes Obes Metab

Dose-finding study of subcutaneous glucagon for hypoglycaemia

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

1 In this article, the authors describe low-dose subcutaneous (SC) glucagon as a potential calorie-free alternative to oral carbohydrate for the treatment of mild hypoglycaemia; however, the optimum dose to recover from a hypo whilst also avoiding rebound hyperglycaemia needs to be determined.

2 Therefore, in this crossover dose-finding study, the authors compared three doses of SC glucagon – 100 µg, 200 µg and 300 µg – to placebo (saline) in eight people with T1D and mild hypoglycaemia.

3 In four separate clinic visits, participants had mild hypoglycaemia (plasma glucose, 3.4 mmol/L) induced through controlled insulin administration. They received the three glucagon doses and placebo in a randomised order, with a washout period of at least 2 days between interventions.

4 Compared with placebo, plasma glucose levels increased significantly by a mean of 2.3, 4.2 and 5.0 mmol/L with the low, medium and high glucagon doses, respectively (final glucose levels, 6.1, 7.9 and 8.7 mmol/L; $P<0.001$).

5 The area under the curve for plasma glucose levels increased with increasing doses; however, the difference between the 200 µg and 300 µg doses was not significant.

6 The authors conclude that low-dose SC glucagon shows promise as a treatment for mild hypoglycaemia, although doses above 200 µg may not achieve significantly better results.

Ranjan A, Schmidt S, Madsbad S et al (2016) Effects of subcutaneous, low-dose glucagon on insulin-induced mild hypoglycaemia in patients with insulin pump treated type 1 diabetes. *Diabetes Obes Metab* **18**: 410–8

Diabet Med

Severe hypoglycaemia and hypoglycaemia unawareness and mortality risk in T1D

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

1 These authors studied the association between severe hypoglycaemia (SH), impaired awareness of hypoglycaemia (IAH) and mortality risk in two cohorts of people with T1D.

2 In the first cohort ($n=269$), from Denmark, IAH was assessed using a questionnaire, a history of lifetime occurrence of SH was recorded and participants were subsequently followed for 1 year to assess SH incidence. Mortality rates over the next 12 years were then assessed.

3 In the second cohort ($n=482$), from the Netherlands, IAH was assessed with a questionnaire, information on SH in the prior year was collected and mortality risk was assessed retrospectively over the next 6.5 years.

4 Annually, SH occurred in 36% of the Danish cohort and 21% of the Dutch cohort. The all-cause mortality rate was 14% ($n=39$) and 4% ($n=20$), respectively.

5 Multivariate analysis showed that neither SH nor IAH was associated with mortality risk in either cohort.

6 These results contrast with findings in people with T2D, in whom even one episode of SH has been linked to death. This discrepancy may be due to the higher rate of cardiovascular comorbidity in people with T2D.

7 These findings suggest that hypoglycaemia does not increase mortality risk in people with T1D, which is important given that the desire to avoid hypoglycaemia may impact optimum glycaemic control.

Sejling AS, Schouwenberg B, Faerch LH et al (2016) Association between hypoglycaemia and impaired hypoglycaemia awareness and mortality in people with type 1 diabetes mellitus. *Diabet Med* **33**: 77–83

ADA 2016

Bihormonal bionic pancreas: Efficacy and safety at home

1 The results of the first trial to assess the safety and effectiveness of continuous, multi-day, automated glycaemic control using insulin and glucagon in a home setting were presented at ADA 2016.

2 A random-order crossover study was conducted to evaluate a bihormonal bionic pancreas against conventional insulin pump therapy in 39 adults with T1D. The participants were living at home and had no restrictions on diet or exercise.

3 Participants spent 11 consecutive days using each of the bionic pancreas (intervention arm) and their own insulin pump (control arm). During the intervention, data from a continuous glucose monitor was used by an autonomously adaptive algorithm to control subcutaneous hormone delivery. While participating in the control arm, individuals managed their own therapy.

4 Use of the bionic pancreas was associated with significant reductions in mean glucose level compared to the control (162±29 vs 141±10 mg/dL [9.0±1.6 vs 7.8±0.6 mmol/L]; $P<0.0001$).

5 The percentage of time spent with blood glucose levels <60 mg/dL (3.3 mmol/L) was also significantly reduced in the intervention arm (1.9%±1.7 vs 0.6%±0.6). The bionic pancreas was also associated with fewer glycaemic events per day than the control.

6 The mean total daily dose of insulin delivered by the bionic pancreas was around 6% more than during the comparator period.

Elkhatib F, Buckingham BA, Buse JB et al (2016) Home use of a bihormonal pancreas vs. conventional insulin pump therapy in adults with type 1 diabetes – a multicenter, randomized clinical trial. *ADA 76th Scientific Sessions*: abstract 77-OR