

Management of type 1 diabetes



Automated closed-loop insulin delivery: The case strengthens

Daniel Flanagan
Consultant Physician, Derriford Hospital, Plymouth

The US Food and Drug Administration has now approved the first fully automated closed-loop insulin delivery system for people with type 1 diabetes. This is a hybrid system requiring the individual to enter mealtime carbohydrates, accept bolus correction dose recommendations and calibrate the sensor with regular capillary glucose readings. The commercial product is likely to be launched in the US in 2017 and Europe in 2018.

We continue to see a steady flow of scientific papers relating to various aspects of automated insulin delivery. This leads to the question of how these products are likely to be first used in the UK. The paper by Stewart and colleagues (summarised alongside) is important, as the group studied must have one of the strongest cases for early use of this expensive technology. Pregnancy is a time when tight glucose control and avoiding hyperglycaemia is especially

important. We already invest a great deal of clinical resource into achieving lower glucose values before and during pregnancy. Having said that, we accept that we will put mother and baby at increased risk of significant hypoglycaemia that may, in itself, have long-term health consequences.

The group compared an overnight closed-loop insulin delivery system with a currently available sensor-augmented pump where the individuals had to make decisions about rate of insulin delivery themselves.

In summary, the study has shown that overnight glucose control improved by a clinically significant amount using the closed-loop system. The improvement seen with the automated system lasts until about midday the following day. This was achieved without any episodes of severe hypoglycaemia in the closed-loop phase of the study. ■

N Engl J Med

Closed-loop system in pregnancy

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

1 There are particular challenges for women with T1D in trying to maintain tight glycaemic control during pregnancy. These include increased insulin requirements and greater variability. Data are lacking on whether closed-loop therapy can help this group.

2 The investigators performed an open-label, randomised, crossover study. Sixteen pregnant women with T1D completed 4 weeks of closed-loop pump therapy (intervention) and sensor-augmented pump therapy (control) in random order. Fourteen women chose to continue using the closed-loop system until after delivery.

3 In the intervention group, the percentage of overnight time that glucose values were within target range was significantly higher than in the control group (74.7% vs 59.5%; $P=0.002$). Furthermore, mean glucose level was significantly lower in the former group, both overnight and over a 24-hour period (6.6 vs 7.4 mmol/L; $P=0.009$).

4 There were no significant differences between groups in time spent below target range, insulin doses or adverse events.

5 Throughout the continuation phase, which included antenatal hospital admission, labour and delivery, glucose levels were within target range 68.7% of the time and mean glucose level was 7.0 mmol/L. There were no episodes of severe hypoglycaemia during either phase.

6 Overnight and day-and-night glucose control was better during closed-loop therapy.

Stewart ZA, Wilinska ME, Hartnell S et al (2016) Closed-loop insulin delivery during pregnancy in women with type 1 diabetes. *N Engl J Med* **375**: 644–54

Diabet Med

Non-severe hypos: frequency and effects

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

1 This UK study set out to quantify the self-reported frequency of non-severe hypoglycaemia and its effects in adults with insulin-treated diabetes.

2 Individuals over 15 years of age with T1D or insulin-treated T2D completed four online questionnaires, one every 7 days. In total, 1038 respondents (466 with T1D and 572 with T2D) completed 3528 questionnaires.

3 The mean numbers of weekly non-severe events was 2.4 for those with T1D and 0.8 for those with T2D; 23% and 26% of such events occurred at night, respectively.

4 The most common features of recent episodes were tiredness/fatigue and reduced alertness. The effects of nocturnal events persisted longer than for daytime events.

5 For those in employment, 20% of events resulted in work-time loss, especially after nocturnal hypoglycaemia.

6 Despite this, most respondents rarely or never informed a healthcare professional. It is likely that the frequency and morbidity of hypoglycaemia is underestimated.

Frier BM, Jensen MM, Chubb BD (2016) Hypoglycaemia in adults with insulin-treated diabetes in the UK: self-reported frequency and effects. *Diabet Med* **33**: 1125–32

Diabetes Care

Severe hypos and islet transplantation

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

- In people with T1D, impaired awareness of hypoglycaemia (IAH) and severe hypoglycaemic events (SHEs) remain causes of substantial morbidity and mortality.
- This phase 3, prospective, open-label, single-arm study, which was conducted at eight centres in North America, evaluated the effectiveness and safety of purified human pancreatic islets (PHPI).
- Participants ($n=48$) were adults with T1D in whom IAH and SHE had persisted despite medical treatment. Each received immunosuppression and one or more transplants of PHPI manufactured onsite.
- The primary endpoint of achievement of HbA_{1c} <53 mmol/mol (7%) and freedom from SHEs was met by 87.5% of subjects at 1 year and by 71% at 2 years. Median HbA_{1c} levels decreased from 55 mmol/mol (7.2%) at baseline to 41 mmol/mol (5.9%) at both 1 and 2 years.
- Hypoglycaemic awareness was restored, as evidenced by marked reductions in Clarke and HYPO scores ($P>0.0001$).
- There were no study-related deaths, although five individuals (10.4%) experienced bleeds and two (4.1%) had infections. Glomerular filtration rate decreased significantly on immunosuppression.
- The authors conclude that islet transplantation should be considered in people with T1D and IAH in whom a stepped-care approach has failed to prevent life-threatening SHEs.

Hering BJ, Clarke WR, Bridges ND et al (2016) Phase 3 trial of transplantation of human islets in type 1 diabetes complicated by severe hypoglycaemia. *Diabetes Care* **39**: 1230–40

Diabetologia

Risk of epilepsy in children with T1D

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

- Epilepsy is a common serious neurological condition that has significant effects on the social and behavioural development of children. Recent studies have revealed that T1D could be a risk factor for its development in children.
- To examine this association, the investigators used population-based data from the Taiwan National Health Insurance Research Database to conduct retrospective cohort analyses.
- In the study cohort, each of 2568 individuals aged 18 years or under with T1D were matched with ten individuals without T1D ($n=25\ 680$) for comparison.
- Incidences of epilepsy were 10.4 and 33.7 per 10 000 person-years for the comparison and T1D individuals, respectively. The risk of individuals in the study cohort developing epilepsy was significantly higher than for those in the comparison group (logrank test, $P=0.0001$). After adjustment for potential confounders, the cohort with T1D was 2.84 times more likely to develop epilepsy than the cohort without.
- The proportion of intellectual disabilities in the T1D cohort was significantly greater than that in the comparison cohort ($P=0.0006$). Furthermore, children with such a disability exhibited a significantly increased risk of epilepsy.
- While the mechanisms of the association between T1D and epilepsy remain unclear and require further investigation, researchers have suggested that hyperglycaemia and hypoglycaemia may have a damaging effect on the central nervous system.

Chou IC, Wang CH, Lin WD et al (2016) Risk of epilepsy in type 1 diabetes mellitus: a population-based cohort study. *Diabetologia* **59**: 1196–1203

Diabetes Care

Fetal diabetes exposure and cognitive function

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

- Between 1993 and 1999, all pregnant women with T1D in Denmark were prospectively reported to a central register.
- The EPICOM (EPigenetic, genetic and environmental effects on Cognitive and Metabolic functions in offspring of mothers with T1D) study used data from the register to examine long-term cognitive consequences of intrauterine hyperglycaemia in adolescent offspring of women with T1D.
- Offspring of a cohort of women with T1D ($n=277$) were examined at 13–19 years of age. A control group from the general population ($n=301$) was also identified. Reynolds Intellectual Assessment Scales were used to evaluate cognitive function.
- Offspring from the diabetes-exposed group had lower scores on all cognitive measures compared with the control group: composite intelligence (95.7 vs 100; $P=0.001$), verbal intelligence (96.2 vs 100; $P=0.004$), non-verbal intelligence (96.4 vs 100; $P=0.008$) and composite intelligence (95.7 vs 100; $P=0.001$).
- Differences in composite intelligence and composite memory remained after adjustment for confounders.
- Parent-reported information about learning difficulty suggested a higher frequency in the diabetes-exposed group.
- The lower cognitive function found in the index group may reflect harmful effects of maternal diabetes on neurodevelopment. The authors recommend early intervention for those at risk of cognitive difficulties.

Bytoft B, Knorr S, Vlachova Z et al (2016) Long-term cognitive implications of intrauterine hyperglycaemia in adolescent offspring of women with type 1 diabetes (the EPICOM Study). *Diabetes Care* **39**: 1356–63

“Islet transplantation should be considered in people with T1D and impaired awareness of hypoglycaemia in whom a stepped-care approach has failed to prevent life-threatening severe hypoglycaemic events.”