Technology

When to use technology: REPOSE, GOLD, DIAMOND and REPLACE-BG provide more evidence

Peter Hammond
Consultant in General Medicine, Harrogate

The REPOSE study (summarised alongside) was designed to test whether initiating insulin pump therapy at the same time as providing structured education for people with type 1 diabetes on multiple daily injection (MDI) therapy resulted in any benefit in terms of HbA_{1c} and episodes of moderate and severe hypoglycaemia.

The conclusion was that there was no improvement in outcomes when pump therapy was added at the same time as Dose Adjustment for Normal Eating (DAFNE) training. Both groups showed an improvement in HbA_{1c} and rates of severe hypoglycaemia. There was a greater reduction in HbA_{1c} in the group starting pump therapy, with the adjusted difference in response being –2.7 mmol/mol (0.24%), but this was not of statistical or clinical significance.

It is crucial to emphasise that the cohort enrolled in the study was not eligible for insulin pump therapy as recommended by NICE (2008) TA151 guidance. NICE recommend insulin pump therapy for people with type 1 diabetes aged ≥12 years who have an HbA_{1c} >69 mmol/mol (8.5%) or disabling hypoglycaemia on MDI therapy despite a high level of care, including the provision of structured education. The outcome of REPOSE supports the current pathway for insulin pump therapy in line with TA151 – that all people should have access to appropriate structured education and, only after this, if HbA_{1c} remains elevated or disabling hypoglycaemia is a problem, should insulin pump therapy be offered.

GOLD, DIAMOND and REPLACE-BG

Three randomised controlled trials of continuous glucose monitoring (CGM) effectiveness have recently been published. What do they tell us about the role of CGM? Insulin pump therapy is supported by a positive NICE technology appraisal, which commissioners are expected to fund. The evidence base for CGM has not been robust enough to date for it to have similar backing, although the NICE (2015) NG17 guideline for adults with T1D does advocate the use of CGM, particularly for those with problematic hypoglycaemia, but also for those with an HbA_{1c} ≥80 mmol/mol (9.5%), provided that CGM results in a fall in HbA_{1c} to <58 mmol/mol (7.5%). This means that insulin pump therapy is the "go-to" option when HbA_{1c} levels are elevated on optimised MDI therapy.

GOLD and DIAMOND make a case for CGM to be given equal consideration, however. In DIAMOND, the HbA_{1c} reduction at 24 weeks was 6.6 mmol/mol (0.6%) greater in the CGM group than the control group, from a mean baseline HbA_{1c} of 70 mmol/mol (8.6%). GOLD was a crossover design, and the mean reduction in HbA_{1c} when using CGM compared to conventional treatment was 4.7 mmol/mol (0.43%) over 26 weeks of usage. While those using CGM are cautioned that they should always use a capillary blood glucose (CBG) measurement for decision-making, in real life, CGM readings are often used for this purpose.

REPLACE-BG considered whether a lack of CBG readings – except for calibration and in a few other specific circumstances where CBG readings might be unreliable – was detrimental to glycaemic control. The CGM-only group performed an average of only 0.8 non-calibration CBG readings daily, but there was no difference in parameters of glycaemic control when compared to those using CGM as an adjunct to regular CBG monitoring.

While insulin pump therapy will probably remain the option of choice when attempting to optimise glycaemic control in those for whom MDI with effective structured education has not achieved HbA_{1c} targets, CGM should be considered as an alternative – particularly for those who have reservations about insulin pump therapy. Improvements in sensor wearability and accuracy mean CGM is an increasingly acceptable alternative, and significant improvements in control can be achieved with a reduced reliance on CBG monitoring. ■

References on following page

BMJ

REPOSE: Pump or MDI therapy for T1D?

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

1 The REPOSE trial compared the effectiveness of insulin pump therapy with multiple daily injections (MDI) for adults with T1D, when added to structured diabetes education.

2 Participants were randomised to receive either pump or MDI therapy for 2 years. Each group attended equivalent DAFNE training courses on flexible intensive insulin treatment at the outset.

3 Results from 260 individuals (132 pump; 128 MDI) were included in the intention-to-treat analysis. After adjustment, the mean reduction in HbA_{1c} at 2 years for those with baseline values ≥58 mmol/mol (7.5%) was 2.7 mmol/mol (0.24%) greater for pump treatment compared with MDI.

4 After 2 years, 25.0% of the pump group and 23.3% of the MDI group achieved an HbA_{1c} ≤58 mmol/mol (7.5%), regardless of baseline value (P=0.57). Severe hypoglycaemic episodes during follow-up were reduced across both groups; rates of reduction did not differ.

5 There were no differences between the groups in most psychosocial measures, but pump users showed greater improvement in treatment satisfaction at 12 and 24 months.

6 While both groups showed clinically relevant decreases in HbA_{1c}, only eight individuals reached the 47 mmol/mol (6.5%) value recommended by NICE.

7 Adding pump treatment to structured training in flexible intensive insulin treatment did not substantially improve education benefits on glycaemic control in adults with T1D.

The REPOSE Study Group (2017) Relative effectiveness of insulin pump treatment over multiple daily injections and structured education during flexible intensive insulin treatment for type 1 diabetes: cluster randomised trial (REPOSE). *BMJ* **356**: j1285

JAMA

CGM lowers HbA_{1c} more in inadequately controlled T1D: GOLD

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

1 Most people with T1D do not achieve recommended glycaemic targets. The GOLD trial evaluated the effects of continuous glucose monitoring (CGM) in 161 adults with T1D and HbA_{1c} >58 mmol/mol (7.5%) who were treated with multiple daily insulin injections.

2 The trial was conducted between February 2014 and June 2016 in 15 diabetes outpatient clinics in Sweden. Participants were randomised to CGM or conventional treatment for 24 weeks, separated by a 17-week washout period. Difference in HbA_{1c} between weeks 26 and 69 was compared for both treatments. Nineteen secondary endpoints were measured.

3 Of the 161 participants, follow-up data for both treatments were available for 142 patients.

4 During CGM, mean HbA_{1c} was 63 mmol/mol (7.9%) and during conventional treatment it was significantly higher, at 68 mmol/mol (8.4%; $P<0.001$). Six secondary endpoints comprising various glycaemic and psychosocial measures significantly favoured CGM compared to conventional treatment.

5 Severe hypoglycaemia occurred in five people in the conventional treatment group and one in the CGM group. Seven people had severe hypoglycaemia during the washout period.

6 The use of CGM in inadequately controlled T1D resulted in lower HbA_{1c} than daily insulin injections.

Lind M, Polonsky W, Hirsch IB et al (2017) Continuous glucose monitoring vs conventional therapy for glycemic control in adults with type 1 diabetes treated with multiple daily insulin injections: the GOLD randomized clinical trial. *JAMA* **317**: 379–87

JAMA

DIAMOND: HbA_{1c} reduction larger with CGM than usual care

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

1 Trials that have shown the benefit of continuous glucose monitoring (CGM) in T1D management have predominantly included adults using insulin pumps, despite the fact that most use insulin injections. The DIAMOND trial compared the effectiveness of CGM with insulin injections in adults with T1D.

2 A total of 105 people using CGM and 53 people using multiple daily insulin injections to control their T1D took part in the study. Participants had HbA_{1c} levels of 58–85 mmol/mol (7.5–9.9%). The primary outcome measure was the change in laboratory-measured HbA_{1c} at 24 weeks.

3 The mean HbA_{1c} reduction from baseline was 12 vs 5 mmol/mol (1.1 vs 0.5%) at 12 weeks and 11 vs 4 mmol/mol (1.0 vs 0.4%) at 24 weeks in the CGM group compared with controls ($P<0.001$).

4 The adjusted treatment-group difference in mean change in HbA_{1c} level from baseline was 7 mmol/mol (0.6%).

5 Median duration of hypoglycaemia at <3.9 mmol/L was 45 min/day in the CGM group and 80 min/day in the control group ($P=0.002$). Severe hypoglycaemia occurred in two people in each group.

6 Compared to usual care with insulin injections, adults with T1D who used CGM had a greater reduction in HbA_{1c} at 24 weeks.

Beck RW, Riddlesworth T, Ruedy K et al (2017) Effect of continuous glucose monitoring on glycemic control in adults with type 1 diabetes using insulin infections: the DIAMOND randomized clinical trial. *JAMA* **317**: 371–8

Diabetes Care

CGM effective with or without BGM

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

1 The REPLACE-BG trial aimed to determine whether continuous glucose monitoring (CGM) without blood glucose monitoring (BGM) is as safe and effective as CGM plus BGM in adults with well-controlled T1D.

2 Adults who had T1D for ≥1 year, HbA_{1c} ≥75 mmol/mol (≥9.0%) and who used an insulin pump were recruited from 14 sites. Before the study, 45% were using CGM.

3 Participants were randomised to CGM only ($n=149$) or CGM plus BGM ($n=77$). Time spent in the target range of 3.9–10.0 mmol/L was the primary outcome.

4 During the trial, average CGM use was 6.7 days/week in the CGM-only group and 6.8 days/week in the CGM plus BGM group. The average number of BGM tests each day (including the two required for CGM calibration) was 2.8 in the CGM-only group and 5.4 in the CGM plus BGM group ($P<0.001$).

5 The mean time in the specified HbA_{1c} range at baseline was 63% in the CGM-only group and 65% in the CGM plus BGM group At 26 weeks, these values remained unchanged in both groups.

6 No severe hypoglycaemic events occurred in the CGM-only group, whereas one occurred in the CGM plus BGM group.

7 The authors conclude that, in adults with well-controlled T1D at low risk of severe hypoglycaemia, the use of CGM without regular confirmatory BGM is as effective and safe as CGM plus BGM.

Aleppo G, Ruedy KJ, Riddlesworth RD et al (2017) REPLACE-BG: A randomized trial comparing continuous glucose monitoring with and without routine blood glucose monitoring in adults with well-controlled type 1 diabetes. *Diabetes Care* **40**: 538–45

"The use of continuous glucose monitoring in inadequately controlled type 1 diabetes resulted in lower HbA_{1c} than daily insulin injections"

References from commentary

NICE (2008) *Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus* [TA151]. NICE, London. Available at: www.nice.org.uk/guidance/ta151 (accessed 19.06.17)

NICE (2015) *Type 1 diabetes in adults: diagnosis and management* [NG17]. NICE, London. Available at: www.nice.org.uk/guidance/ng17 (accessed 19.06.17)