Technology

Continuous subcutaneous insulin infusion: Superior to multiple daily injections in type 2 diabetes?

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When evaluating the indications for insulin pump therapy in their last appraisal, NICE (2008) stated that insulin pump therapy is not recommended for the treatment of people with type 2 diabetes. This reflected the evidence from randomised controlled trials comparing multiple daily injections of insulin (MDI) with insulin pump therapy (continuous subcutaneous insulin infusion [CSII]). Two large trials with parallel treatment arms showed no difference in HbA_{1c} improvement between CSII and MDI, nor any difference in weight change (Raskin et al, 2003; Herman et al, 2005). However, baseline HbA_{1c} in both these trials was between 8.0% and 8.5%, and although subjects were taking insulin prior to the study, they were not required to be on intensive insulin therapy.

Two much smaller trials, using a crossover design, had conflicting results in terms of HbA_{1c} reduction, one in favour of CSII, the other in favour of MDI, again with no difference in weight change between the two treatments (Wainstein et al, 2005; Berthe et al, 2007). However, evidence from case reports has suggested that in the subgroup of patients with type 2 diabetes on intensive insulin regimens but achieving poor glycaemic control and/or requiring large insulin doses, CSII can be very effective at improving glycaemic control, with considerably reduced insulin requirements (Reznik and Cohen, 2013). The benefit of CSII in this situation is likely to be because the volume of insulin in the subcutaneous tissue at any one time is considerably reduced when using CSII compared with MDI and, therefore, the absorption of insulin is more reliable and predictable.

The apparent flaw in previous studies was the patient groups enrolled. In the OpT2mise study (summarised alongside), Reznik et al recruited patients with type 2 diabetes who had poor glycaemic control (HbA_{1c} 64–108 mmol/mol [8.0–12.0%]) despite high-dose MDI with insulin analogues (0.7–1.8 units per kg body weight, maximum dose 220 units). The mean HbA_{1c} at baseline was 75 mmol/mol (9%) and the average total daily insulin dose was 1.1 units per kg body weight. After 6 months, patients who were randomised to CSII had a reduction in HbA_{1c} of 1.1% compared with 0.4% for those randomised to MDI. Overall, 55% of CSII users achieved an HbA_{1c} of <8.0%, compared with 28% of MDI users. The total daily dose of insulin was significantly lower at the study end for CSII users compared with MDI users (97 units vs 122 units). There was no difference between the groups in terms of weight change during the study period. In the CSII users, the basal:bolus ratio increased from 1.2 at baseline to 1.7 at study end. There was inconsistent use of the pump bolus calculator function, but this did not appear to influence the improvement in HbA_{1c}.

The OpT2mise study confirms the potential benefit of CSII over MDI in type 2 diabetes and gives a clear indication for when to consider CSII: in people who are on MDI requiring large doses of insulin (probably in excess of 100 units/day) and with poor glycaemic control (HbA_{1c} >8.0%). When CSII is used, expect most of the insulin, probably 60–65%, to be delivered via basal infusion. While the upper limit of the insulin dose for the participants in this study was 220 units, anecdotal evidence would suggest that there is no upper limit for insulin dose above which CSII is likely to be less effective than MDI; indeed, patients on higher doses may do even better in practice than the patients included in this landmark study. ■

Berthe E et al (2007) *Horm Metab Res* **39**: 224–9

Herman WH et al (2005) *Diabetes Care* **28**: 1568–73

NICE (2008) *Technology Appraisal 151*. NICE, London. Available at: http://www.nice.org.uk/guidance/ta151 (accessed 24.10.14)

Raskin P et al (2003) *Diabetes Care* **26**: 2598–603

Reznik Y, Cohen O (2013) *Diabetes Care* **36**(Suppl 2): S219–25

Wainstein J et al (2005) *Diabet Med* **22**: 1037–46

Lancet

CSII superior to MDI in people with poorly controlled T2D

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

1 OpT2mise was a 6-month, multicentre study to compare multiple daily injections (MDI) with continuous subcutaneous insulin infusion (CSII) therapy in people with T2D and poor glycaemic control despite optimised treatment with insulin analogues.

2 Upon completing a 2-month dose-titration period, participants who still had an HbA_{1c} of 8.0–12.0% (64–108 mmol/mol) were randomised to CSII (n=168) or MDI (n=163).

3 Baseline characteristics were similar in the two groups, including a mean HbA_{1c} of 75 mmol/mol (9.0%). After 6 months of treatment, there was a significantly greater reduction in HbA_{1c} in the CSII group (1.1% vs 0.4%; P<0.001).

4 The proportion of people who achieved an HbA_{1c} of ≤8% was also greater in the CSII group (55% vs 28%; P<0.001).

5 At the end of the study, the total daily dose (97 vs 122 units) and daily basal dose (52 vs 61 units) were significantly lower in the CSII group.

6 Five episodes of hyperglycaemia related to the pump occurred in the CSII group but did not require hospitalisation. Three episodes of severe hypoglycaemia (two in the CSII group and one in the MDI group) and one episode of severe hypoglycaemia (in the MDI group) occurred.

7 Overall, 38% of participants in the CSII group had evidence of mild cognitive impairment, suggesting that pump therapy can also be effective in such a patient group.

Reznik Y, Cohen O, Aronson R et al (2014) Insulin pump treatment compared with multiple daily injections for treatment of type 2 diabetes (OpT2mise): a randomised open-label controlled trial. *Lancet* **384**: 1265–72

J Clin Endocrinol Metab

CGM in women with gestational diabetes

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

1 The authors sought to determine whether the addition of continuous glucose monitoring (CGM) to a standard self-monitoring of blood glucose (SMBG) routine could improve the pregnancy outcomes of women with gestational diabetes mellitus (GDM).

2 A total of 340 Chinese women with oral glucose tolerance test-confirmed GDM were randomised either to standard antenatal care using finger-prick SMBG seven times per day (n=190) or to standard care, SMBG and CGM (n=150).

3 Participants in the CGM group underwent a 3-day period of CGM every 2–4 weeks, and all participants attended the clinic each week for adjustment of therapy (including diet, lifestyle and medication), which was based on SMBG data alone in the control group and combined SMBG and CGM data in the intervention group.

4 After 5 weeks, measures of glycaemic variation (determined with a 3-day CGM study in both groups) were significantly lower in the CGM group (e.g. mean amplitude of glycaemic excursions [MAGE], 1.8 vs 2.4 mmol/L). The risks of pre-eclampsia (3.4% vs 10.1%) and primary caesarian delivery (34.7% vs 46.6%) were also lower in the CGM group.

5 MAGE after 5 weeks was independently associated with pre-eclampsia (odds ratio [OR], 3.66), macrosomia (OR, 1.90) and neonatal hypoglycaemia (OR, 1.63).

6 Supplementing CGM to routine antenatal care appears to improve glycaemic control and pregnancy outcomes in women with GDM.

Yu F, Lv L, Liang Z et al (2014) Continuous glucose monitoring effects on maternal glycemic control and pregnancy outcomes in patients with gestational diabetes mellitus: a prospective cohort study. *J Clin Endocrinol Metab* 24 Jul [Epub ahead of print]

Diabetes Metab Res Rev

Treatment modalities and axonal function in people with T1D

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

1 Compared with those with T2D, people with T1D can develop a more severe phenotype of peripheral neuropathy.

2 In this study, 41 people with T1D without clinical signs of diabetic neuropathy underwent nerve excitability testing to determine whether there were any preclinical differences in axonal function, and to determine whether treatment with continuous subcutaneous insulin infusion (CSII) or multiple daily insulin injections (MDI) had any effect on this.

3 There were 17 participants receiving CSII and 24 receiving MDI. Compared with both the CSII group and 20 age- and gender-matched controls, the MDI group had prominent abnormalities in axonal function.

4 The pattern of change indicated axonal membrane depolarisation and was consistent with previous studies in people with T1D.

5 Further evaluation conducted 6–12 months later in a subgroup of the cohort showed that the abnormalities persisted in the MDI group (n=12) but remained absent in the CSII group (n=6).

6 The authors hypothesise that these differences may have been a result of the lower glycaemic variability that is typically achieved with CSII, and the subsequent reduction in oxidative stress and microvascular dysfunction.

7 Longer follow-up will be needed to determine whether this has any effect on outcomes; however, these findings suggest that CSII may have a neuroprotective effect in T1D.

Kwai N, Arnold R, Poynten AM et al (2014) Continuous subcutaneous insulin infusion preserves axonal function in type 1 diabetes mellitus. *Diabetes Metab Res Rev* 28 Jul [Epub ahead of print]

Diabetes Care

CGM use in the T1DX clinic registry

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

1 The authors report on the frequency of continuous glucose monitoring (CGM) use in the T1DX (T1D Exchange) registry, as well as the outcomes associated with its use.

2 Among 17 317 responding participants, 1613 (9%) used CGM. Its use was more common in people with a higher education level, higher income, private health insurance, longer diabetes duration and use of an insulin pump.

3 In adults and children, but not adolescents or young adults, CGM use was associated with a lower mean HbA_{1c}. After adjustment for demographics, CGM use had no effect on the incidence of severe hypoglycaemia or diabetic ketoacidosis.

4 The real-time CGM features were judged to be more useful than the retrospective features; only 46% found the latter features helpful, while 28% thought they were actively unhelpful.

5 The discontinuation rate was high, at 41% over the 1-year follow-up. The most common reasons were discomfort while wearing the device (42% of those who discontinued), problems with inserting or maintaining the sensor in place (30–33%), too many alarms (28%) and concerns about accuracy (25%).

6 HbA_{1c} reduction was more likely in those who used CGM for ≥6 days per week. This, along with the fact that HbA_{1c} tended not to improve in adolescents and young adults, who typically have lower compliance, suggests that future CGM development should work to improve compliance and improve the factors that lead to discontinuation.

Wong JC, Foster NC, Maahs DM et al (2014) Real-time continuous glucose monitoring among participants in the T1D Exchange clinic registry. *Diabetes Care* **37**: 2702–9

> *"Supplementing continuous glucose monitoring to routine antenatal care appears to improve glycaemic control and pregnancy outcomes in women with gestational diabetes."*