Management of type 1 diabetes

Insulin underdelivery: A frequently overlooked cause of poor glycaemic control

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Recently I had a patient with insulin-treated type 2 diabetes who arrived at the consultation with the declaration "I think I've found out what the problem is." I breathed a sigh of relief because for the last two years I'd groaned (hopefully internally) whenever she'd walked into the diabetes clinic.

She had resisted insulin therapy for years despite ghastly control on everything else we had thrown at her. Initially she did reasonably well on a twice-daily fixed mixture of soluble and isophane human insulin, but she admitted to a mild needle phobia and, unbeknownst to me, had been switched to guarded insulin pen needles. The dose of insulin was cranked up but her HbA_{1c} continued to rise. Following an admission to hospital with urosepsis, she became repeatedly hypoglycaemic when nursing staff administered her usual insulin dose. I suspected insulin omission at home but she, her husband and her daughter all strongly denied this. Her HbA_{1c} remained above 100 mmol/mol (11.3%) and the same thing happened during her next admission.

It was only when the locum GP gave her the wrong pen needles and she started having repeated hypos at home that the penny dropped. Whatever she had been doing previously had resulted in non-delivery of part or all of her insulin doses. She had to reduce her dose by 60% and thereafter her HbA_{1c} fell to a passable 68 mmol/mol (8.4%).

The paper by Joubert et al (summarised alongside) illustrates another potential cause of insulin underdelivery – withdrawing the needle from the skin too soon after the injection – and illustrates the importance of both teaching and observing insulin injection technique. Lipohypertrophy, wrong-sized needles, premature insulin withdrawal and difficulties with plunger depression all contribute to the vagaries of insulin action and should be considered by all healthcare professionals when contemplating causes of inadequate diabetes control. This is an important but often overlooked factor. ■

Diabet Med

Insulin degludec superior to glargine in terms of nocturnal hypoglycaemia

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

1 A previous meta-analysis of the phase III trials comparing the basal insulins degludec and glargine showed that the former was associated with lower rates of nocturnal hypoglycaemia (blood glucose <3.1 mmol/L). This *post hoc* analysis made the same comparisons using different definitions of hypoglycaemia and timescales for the nocturnal period.

2 Generally, in 1122 people with T1D, rates of nocturnal hypoglycaemia remained lower with insulin degludec by between 97 and 203 episodes per 100 person-years, depending on the definitions of hypoglycaemia and the nocturnal period.

3 The one exception was when the nocturnal period was defined as 00.01–07.59. Here, the nocturnal hypoglycaemia rate was 2 episodes per 100 person-years higher with insulin degludec, a 2.5-fold increase compared with other definitions.

Heller S, Mathieu C, Kapur R et al (2015) A meta-analysis of rate ratios for nocturnal confirmed hypoglycaemia with insulin degludec vs. insulin glargine using different definitions for hypoglycaemia. *Diabet Med* 20 Oct [Epub ahead of print]

Diabetes Technol Ther

Premature needle withdrawal significantly affects insulin delivery

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

1 In this laboratory-based study, the authors sought to quantify insulin underdelivery as a result of withdrawing the needle prematurely.

2 Three prefilled insulin pens (Kwikpen, Flexpen and Solostar) and three reusable pens (Humapen, Novopen and JuniorSTAR) were evaluated, all using 4-mm needles and delivering doses of 5 units and 10 units.

3 A single investigator pressed the injection button with maximum thumb strength for a total of 10 seconds. Insulin underdelivery, defined as the amount of insulin delivered in the final 8 seconds and 7 seconds for the 5-unit and 10-unit doses, respectively, was measured.

4 With prefilled pens using the 5-unit dose, insulin underdelivery ranged from 0.22 to 1.01 units depending on the pen and insulin type, representing 4.4–20.2% of the intended dose.

5 The amount of undelivered insulin was lower in the reusable pens, ranging from 0.15 to 0.43 units (3.0–8.6% of the intended dose).

6 Insulin underdelivery was also lower at the 10-unit dose, ranging from 2.8% to 10.7% of the intended dose in prefilled pens and from 1.6% to 4.1% in the reusable pens.

7 These findings demonstrate the importance of teaching correct injection technique, including keeping the needle under the skin for sufficient time after injection. The appropriate time ranges from 5 to 10 seconds according to the instructions of the various pens.

Joubert M, Haddouche A, Morera J et al (2015) Potential insulin underdelivery from prefilled and reusable insulin pens in cases of premature needle withdrawal: a laboratory evaluation. *Diabetes Technol Ther* **17**: 712–6

"These findings suggest that both men and women with type 1 diabetes have an increased risk of fracture and thus may need earlier screening for osteoporosis."

Diabetes Obes Metab

Strategies to avoid exercise-induced hypoglycaemia in pump users

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

1 In this single-blind, crossover study, the authors compared a number of strategies to avoid exercise-induced hypoglycaemia by reducing insulin infusion rates in 20 adults with T1D on insulin pump therapy.

2 On separate days, in a randomised order, participants underwent either moderate- or high-intensity exercise (50% or 75% of maximum oxygen consumption, respectively) 3 hours after lunch.

3 In the afternoons following medium-intensity exercise, compared with an exercise-free day, reducing the basal insulin rate by 80% throughout the exercise period and the following 2 hours was found to prevent an increase in hypoglycaemic events (blood glucose <3.3 mmol/L), whereas more episodes occurred if the basal rate was reduced by only 50%.

4 Similarly, completely suspending the basal infusion prevented hypoglycaemia with high-intensity exercise, whereas reducing the rate by 80% did not.

5 A second study conducted 90 minutes after lunch showed a trend (P=0.07) towards reduced hypoglycaemia by lowering the bolus dose compared with lowering the basal rate.

6 Irrespective of dose reduction or exercise regimen, mean blood glucose fell by around 3.3 mmol/L after 30 minutes of exercise, remaining stable until the next morning with no rebound hyperglycaemia.

Franc S, Daoudi A, Pochat A et al (2015) Insulin-based strategies to prevent hypoglycaemia during and after exercise in adult patients with type 1 diabetes on pump therapy: the DIABRASPORT randomized study. *Diabetes Obes Metab* **17**: 1150–7

Diabetes Care

Canagliflozin in addition to insulin in T1D: phase II study

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

1 In this multicentre, phase II study, the efficacy and safety of the sodium–glucose cotransporter 2 inhibitor canagliflozin was compared with placebo as an adjunct to insulin therapy in adults with T1D.

2 A total of 351 people were randomised to receive canagliflozin 100 mg, 300 mg or placebo alongside their insulin regimen, titrated to achieve pre-meal and bedtime glucose levels of 4.4– 6.7 mmol/L.

3 After 18 weeks of therapy, the primary endpoint – a reduction in HbA_{1c} of ≥4 mmol/mol (0.4%) with no increase in body weight – was achieved in 36.9%, 41.4% and 14.5% of people in the 100 mg, 300 mg and placebo groups, respectively (P<0.001 for both comparisons).

4 Canagliflozin also resulted in reductions in body weight (3.4–5.3%), fasting plasma glucose (0.5–0.6 mmol/L) and total insulin dose (4.1–7.6 units per day) compared with placebo.

5 Hypoglycaemia rates were similar between the groups, with severe hypoglycaemia rates of 1.7–6.8%).

6 The incidence of serious adverse events was 7.7%, 6.8% and 0% with canagliflozin 100 mg, 300 mg and placebo, respectively.

7 These included diabetic ketoacidosis (DKA), which occurred in 4.3% (n=5) of the 100 mg group and 6.0% (n=7) of the 300 mg group. DKA was euglycaemic in five participants, and all cases of DKA had precipitating factors (e.g. illness or insulin pump failure).

Henry RR, Thakkar P, Tong C et al (2015) Efficacy and safety of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to insulin in patients with type 1 diabetes. *Diabetes Care* **38**: 2258–65

Diabet Med

Increased fracture risk in people with T1D

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

1 In this systematic review and meta-analysis, the authors determined the association between T1D and risk of fractures.

2 In a total of 14 studies evaluated, there were 2066 fractures in 27 300 people with T1D (7.6%) compared with 136 579 among 4 364 125 people without T1D (3.1%).

3 The pooled relative risk (RR) of any fracture was 1.36 (95% confidence interval, 1.51–6.63).

4 Heterogeneity was high (I^2=98.25); however, the difference remained significant in sensitivity analyses in which outliers and various study types were excluded (RRs ranging from 1.54 to 4.45).

5 The pooled RR was 3.78 for hip fracture and 2.88 for spinal fracture in people with T1D compared to those without the condition.

6 Fracture risk was greater in women with T1D than men with the condition (RR, 4.10 vs 1.79 for any fracture; 5.19 vs 4.05 for hip fracture; 2.65 vs 1.73 for fractures other than hip) compared with the general population.

7 The authors propose several mechanisms behind this risk, including reduced bone mineral density in childhood and adolescence in T1D, which may result in osteoporosis in later life; and an increased risk of autoimmune diseases (e.g. coeliac disease and thyroid disease) that are also associated with fracture risk.

8 These findings suggest that both men and women with T1D have an increased risk of fracture and thus may need earlier screening for osteoporosis.

Shah VN, Shah CS, Snell-Bergeon JK (2015) Type 1 diabetes and risk of fracture: meta-analysis and review of the literature. *Diabet Med* **32**: 1134–42