# Management of type 1 diabetes

## *Is glucagon-like peptide-1 analogue therapy helpful in type 1 diabetes?*

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The results of the study by Frandsen and colleagues (summarised alongside) are essentially negative, but the study may still be helpful. Over the past few years, new therapies have transformed the treatment of type 2 diabetes. New classes of medications have allowed us to control blood glucose with a reduced risk of hypoglycaemia and weight gain. For some patient groups, hypoglycaemia represents a high clinical risk. Weight gain is likely to translate into increased cardiovascular risk; it therefore follows that reduced weight gain is likely to translate into reduced cardiovascular risk – although we await definitive studies showing this.

Glucagon-like peptide-1 (GLP-1) receptor agonist therapy has proven to be one of the more powerful tools we have in type 2 diabetes. The longer-term studies that have now been published suggest that GLP-1 analogue therapy, alone or in combination with insulin, results in improved glucose control and reduced weight gain over time when compared with insulin therapy alone. Defining the specific group of people with type 2 diabetes who will benefit most is more difficult. Taking this further, the evidence that GLP-1 analogues may benefit individuals with type 1 diabetes is even more tenuous.

It is perhaps worth considering why we might want to consider using GLP-1 analogues in type 1 diabetes. What could be the possible benefits? This class of medications have undoubted benefits in reducing weight gain and have been shown to reduce insulin dose requirements in overweight, insulin-resistant subjects. We might, therefore, want to study a group of overweight individuals with type 1 diabetes and high insulin requirements.

One of the key features of type 2 diabetes is dysregulation of glucagon secretion, with overproduction of glucagon after meals. Frandsen and colleagues suggest that this is also a problem in type 1 diabetes, but actually the evidence for this is not clear. There is a strong suggestion that glucagon secretion is, in fact, downregulated in long-standing type 1 diabetes (although the evidence mostly relates to hypoglycaemia). The study population here comprised normal-weight individuals, and glucagon secretion was not measured. Although the overall conclusion was that there was no major benefit in this patient group, this does not rule out the possibility that GLP-1 analogues may help a subgroup of people with type 1 diabetes. ■

## Diabetes Care

### Liraglutide in T1D: Weight reduced but no change in $HbA_{1c}$

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

1 In this double-blind, placebo-controlled trial, 40 people with T1D, normal weight and suboptimal glycaemic control ($HbA_{1c}$, ≥64 mmol/mol [8.0%]) were randomised to liraglutide 1.2 mg or placebo in conjunction with their usual insulin regimen.

2 After 12 weeks, mean $HbA_{1c}$ reduced significantly in both groups; however, there was no significant difference between liraglutide and placebo (mean reduction, 6.2 vs 5.6 mmol/mol [0.6% vs 0.5%]).

3 Furthermore, glycaemic variability remained similar in the two groups, regardless of which method was used to estimate it.

4 However, body weight decreased in the liraglutide group while it increased in the placebo group (mean change, –3.1 kg vs +1.1 kg; $P<0.001$).

5 There was also a small but significant reduction in bolus insulin requirements in the liraglutide group (mean reduction, 4.0 units vs 0.0 units; $P=0.02$).

6 Heart rate increased significantly, by around 3 bpm, in the liraglutide group; however, the difference compared with placebo was not significant.

7 Adverse events, mostly gastrointestinal, occurred in 90% of liraglutide recipients and 65% of placebo recipients but were mostly transient.

8 The authors conclude that liraglutide 1.2 mg has little effect on $HbA_{1c}$ but a significant effect on weight loss when added to insulin therapy in normal-weight people with T1D.

Frandsen CS, Dejgaard TF, Holst JJ et al (2015) Twelve-week treatment with liraglutide as add-on to insulin in normal-weight patients with poorly controlled type 1 diabetes: a randomized, placebo-controlled, double-blind parallel study. *Diabetes Care* **38**: 2250–7

ADA 2016

## DIaMonD: CGM benefits for MDI users


1 A session at ADA 2016 presented the results of the first stage of the DIaMonD study. This stage was designed to assess whether the addition of continuous glucose monitoring (CGM) for adults with T1D on multiple daily injection (MDI) therapy is beneficial. Around 15% of CGM users are on MDI therapy.

2 Participants with poor glycaemic control (average $HbA_{1c}$, 70 mmol/mol [8.6%]) were randomised to receive CGM ($n$=105) for 24 weeks or to continue use of their usual blood glucose meter ($n$=53).

3 Following the intervention, $HbA_{1c}$ in the CGM group had declined by 9.8 mmol/mol (0.9%) from baseline compared to a lesser improvement of 4.4 mmol/mol [0.4%] in the control group ($P$<0.001).

4 Furthermore, CGM reduced the amount of time spent per day with blood glucose <3.9 mmol/L by 30% (–23 minutes; $P$=0.006), while usual care reduced it by 17% (–15 minutes). With CGM, time spent per day >10.0 mmol/L showed a 12% improvement (–83 minutes) and the amount of time spent in range per day increased by 11% (72 minutes).

5 Glycaemic variability significantly improved by 4% with CGM compared to the control, which showed no change ($P$<0.001).

6 The authors concluded that clinicians should consider recommending CGM to all people with T1D who have not attained their glycaemic goals.

McGill JB, Ahmann AJ, ToschiE, Wolpert HA (2016) The value of continuous glucose monitoring in patients with type 1 diabetes using multiple daily injections. *ADA 76th Scientific Sessions*: Session 3-CT-SY30

Diabetes Care

## The importance of resuspending NPH insulin before injection

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

1 Neutral protamine Hagedorn (NPH) insulin comes in a two-phase solution with either a solvent or a rapid-acting insulin and requires mixing to achieve complete resuspension before injection.

2 These authors compared NPH pharmacokinetics and pharmacodynamics following injection after either adequate resuspension (tipping the pen 20 times) or keeping the pen horizontal or vertical with the tip either up or down. Eleven people with T1D were studied with a euglycaemic clamp in a randomised, crossover design.

3 Compared with resuspended NPH, plasma insulin concentrations significantly reduced when the pen was kept horizontal or tip-up (peak levels approximately 15 vs 22 microunits/mL) and significantly increased when the pen was kept tip-down (~26 vs 22 microunits/mL).

4 Similarly, the glucose infusion rate required to maintain the euglycaemic clamp was significantly higher with the tip down, and significantly lower with the tip up or horizontal.

5 Compared with the resuspended insulin (11.8 hours), the duration of insulin action was shorter with the horizontal (10.1 hours) and tip-up pen (9.4 hours), and longer with the tip-down pen (15.4 hours).

6 These differences could translate to hypo- or hyperglycaemia in practice, and they reinforce the importance of resuspending NPH insulin.

Lucidi P, Porcellati F, Marinelli Andreoli A et al (2015) Pharmacokinetics and pharmacodynamics of NPH insulin in type 1 diabetes: the importance of appropriate resuspension before subcutaneous injection. *Diabetes Care* **38**: 2204–10

Diabetes Care

## Lipid-lowering therapies, CVD and death in T1D

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

1 The investigators set out to evaluate the effect of lipid-lowering therapy (LLT) in the primary prevention of cardiovascular disease (CVD) and death in individuals with T1D.

2 A nationwide longitudinal cohort study was conducted. The Swedish National Diabetes Register was used to identify a cohort of 24 230 individuals with T1D but no history of CVD. Of these, 18 843 were untreated and 5387 were treated with LLT (97% of these with statins).

3 The cohort was followed for a mean of 6.0 years. Propensity scores for LLT treatment were calculated from 32 baseline clinical and socioeconomic variables. After balancing all 32 covariates using the propensity scores, there were no differences between the two groups.

4 Calculations then revealed the following hazard ratios for treated vs untreated: CV death, 0.60 (95% confidence interval, 0.50–0.72); all-cause death, 0.56 (0.48–0.64); fatal/non-fatal stroke, 0.56 (0.46–0.70); fatal/non-fatal acute myocardial infarction, 0.78 (0.66–0.92); fatal/non-fatal coronary heart disease, 0.85 (0.74–0.97); and fatal/non-fatal CVD, 0.77 (0.69–0.87).

5 LLT was associated with a 22–44% reduction in the risk of CVD and CV death among individuals with T1D and without a history of CVD.

6 This study underlines the importance of intervention with LLT in primary prevention to reduce cardiovascular risk in people with T1D.

Hero C, Rawshani A, Svensson AM et al (2016) Association between use of lipid-lowering therapy and cardiovascular diseases and death in individuals with type 1 diabetes. *Diabetes Care* **39**: 996–1003

***"The authors conclude that liraglutide 1.2 mg has little effect on $HbA_{1c}$ but a significant effect on weight loss when added to insulin therapy in normal-weight people with type 1 diabetes."***