GLP-1 analogue use in patients with sub-optimally controlled type 1 diabetes or obesity improves weight and HbA1c

Abstract
GLP-1 analogues are licensed for add-on therapy for patients with type 2 diabetes who have sub-optimal glycaemic control on other glucose lowering agents. Their use in patients with type 1 diabetes has been evaluated in primarily research settings. We investigated the effect of adding GLP-1 analogues on weight and glycaemic control in our patients with type 1 diabetes.

A retrospective observational case note review of patients with type 1 diabetes between 2011 and 2014 was performed to recruit patients to this study. Inclusion criteria were established treatment with multiple daily injections or continuous subcutaneous insulin infusion and sub-optimal glycaemic control (HbA1c >57mmol/mol or obesity (BMI >30kg/m²)). A GLP-1 analogue was added to pre-existing treatment. HbA1c and weight were measured at initiation and six monthly for up to 30 months.

Thirty-three patients were included. The addition of a GLP-1 analogue significantly improved mean HbA1c from baseline at 6, 12 and 30 months (79mmol/mol, 71mmol/mol, 70mmol/mol; all p<0.05); and weight from baseline at 6, 12, 18, 24 and 30 months (104.9kg, 98.0kg, 98.5kg, 94.7kg, 92.0kg; all p<0.05). Patients with BMI <35kg/m² had an improved response in both weight and HbA1c over those with BMI ≥35kg/m². Three patients discontinued treatment due to gastrointestinal side effects.

In conclusion, the addition of a GLP-1 analogue to existing treatment resulted in significantly improved glycaemic control and weight loss in patients with type 1 diabetes.

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Key words
type 1 diabetes; GLP-1 analogue

Introduction
Achieving good glycaemic control is extremely difficult for some patients with type 1 diabetes putting them at significant risk of complications. Intensive insulin therapy in type 1 diabetes (T1DM) can be associated with weight gain for two reasons: the non-physiological pharmacokinetic and metabolic profiles that follow subcutaneous administration of insulin, and a higher rate of hypoglycaemia which can lead to increased calorie intake.

As with the general population, higher BMI in people with T1DM is associated with increased morbidity and mortality. Excess weight gain in the Diabetes Complications and Control Trial was associated with more extensive atherosclerosis during the prolonged follow-up EDIC study with the so-called ‘double diabetes’ effect.

Weight loss in people with T1DM can be difficult to initiate and maintain due to the reasons and treatment regimens described above, and may be contributed to by disordered eating and a complex relationship with food.

The added complexity of matching reduced insulin with reduced carbohydrate intake and undertaking physical activity while balancing glycaemia all contribute to making weight loss difficult. While most medical therapies in the management of diabetes increase weight, there are a limited number of drugs which have proven to have some benefit as add-on therapy to lifestyle for weight loss in type 2 diabetes (T2DM).

Incretins are a group of gut derived hormones involved in glucose regulation. The peptide hormone GLP-1 mediates the incretin pathway leading to lower postprandial glucose levels via multiple mechanisms. They act by increasing insulin secretion and decreasing glucagon secretion from the pancreas following nutrient ingestion. GLP-1 analogues are known to hold extrapancreatic effects including slowing the rate of gastric emptying and reducing gastric acid secretion resulting in a
decrease of the postprandial glucose peak. GLP-1 receptors have also been localised to hypothalamic nuclei important for the regulation of satiety. Currently, GLP-1 analogues are not licensed for T1DM. The potential for improving glycaemic control through these mechanisms of action is also highly relevant in T1DM, however – particularly the down-regulation in glucagon production by the alpha cells of the pancreas, the reduced rate of gastric emptying and increased satiety. There are several different drugs within the class and they have been adopted widely. They have been proven to be effective for weight loss and improved glycaemic control in patients with T2DM, and certain patients with T1DM may have similar benefits.

There is an emerging role for the use of GLP-1 analogues in obese individuals without diabetes, and the use of liraglutide for overweight and obesity has now been given Food and Drug Administration approval in the USA. Currently, there is limited evidence for the use of GLP-1 analogues in T1DM. Early trial evidence suggests a role for GLP-1 receptor agonists in people with T1DM, with small preliminary studies reporting weight reduction and improved glycaemic control. While no longer-term follow up or large cohort studies exist to date, large, prospectively randomised studies have started to investigate the role of liraglutide as an additional treatment in T1DM and we wait for these to report. Since 2011, we have been using GLP-1 analogues in selected, motivated patients with poor glycaemic control, or in those who would particularly benefit from weight loss. Others with similar practice have demonstrated benefit in small numbers of patients over short time periods. Here we present the first longer-term data for the novel use of GLP-1 analogues in T1DM.

Methods
We carried out a retrospective observational case note review of our patients with T1DM who were started on a GLP-1 analogue between 2011 and 2014. Inclusion criteria were: T1DM, established treatment with multiple daily injections or continuous subcutaneous insulin infusion (CSII), sub-optimal glycaemic control (HbA1c >57mmol/mol), or obesity (BMI >30kg/m2) or progressive weight gain. Appropriate patients were started on a GLP-1 analogue between 2011 and 2014 following consultation at a specialist T1DM or insulin pump clinic at the Royal Bournemouth Hospital. Patients were selected based on engagement with the service and willingness to add another injectable therapy to treatment. All patients were fully counselled about the unlicensed use of GLP-1 analogues in T1DM and patients with previous pancreatitis, with risk factors for the development of pancreatitis, or with a personal or family history of medullary thyroid carcinoma were excluded. Informal consent was obtained. Patients were commenced on either liraglutide 0.6mg initially and titrated to 1.2–1.8mg as tolerated or exenatide, either standard (20μg bd) or prolonged release (2mg once weekly), in addition to pre-existing treatment. The choice of agent was based on patient preference. Prescriptions for the first 28 days were provided by secondary care and thereafter were continued in primary care with agreement from the primary care prescriber. Patients were followed up six monthly and had open access to clinics when required. Consideration was given to a reduction in insulin dose on an individual

![Flow chart showing length of GLP-1 analogue treatment and reasons for discontinuing](image-url)
basis according to initial HbA1c and the frequency and severity of hypoglycaemia. The primary endpoints were improved glycaemic control (HbA1c reduction of 5mmol/mol) and/or sustained weight loss of >5%. If neither endpoint was attained by six months, the GLP-1 analogue was withdrawn. All females of child bearing age were counselled on the need for reliable contraception while using a GLP-1 analogue and for six months after its discontinuation, and were counselled about the lack of evidence on the safety of this class of drugs in pregnancy. This was re-iterated at each follow-up visit and continues to be discussed at each consultation.

Statistical analysis was performed using Student’s t-test and multiple regression analysis with weight as a covariate where appropriate using SPSS v17.0. Analysis was on an intention-to-treat basis. Subgroup analysis was carried out using the WHO criteria for class II obesity (BMI 35kg/m²) as a cut off.22

### Results

Thirty-three patients were started on GLP-1 analogues between 2011 and 2014. Median baseline parameters were: age 51.5 years (range 19–73), weight 104.9 kg (83.2–135.4), BMI 34.5kg/m² (28.3–53.9), and HbA1c 79.0mmol/mol (45–123). Ten patients were already established on CSII therapy. Twenty-eight patients (85%) were started on liraglutide (titrated to 1.2–1.8mg, median dose 1.2mg od) and five on exenatide (three on prolonged release and two on standard formulation). The mean time to total follow up was 16 months (range 6–30).

All patients successfully completed at least six months of GLP-1 analogue treatment at the time of their last review. Nineteen (58%) had completed 12 months, 14 (42%) 18 months, 13 (39%) 24 months and eight (24%) have had GLP-1 analogue therapy for 30 months at the end of current follow-up period (Figure 1). Three patients (9%) discontinued treatment due to gastrointestinal side effects at the first formal review; one patient died from cervical cancer, one patient had a kidney/pancreas transplant so was withdrawn at the point of transplant. After 12 months’ therapy, no patient discontinued GLP-1 use due to side effects.

The addition of a GLP-1 analogue significantly improved mean HbA1c from baseline to six months (79 to 71mmol/mol, p=0.03; Table 1, Figure 2), and this was maintained at 12 months (70mmol/mol, p=0.001). From this time point HbA1c levels increased but remained under baseline levels with values at 18, 24 and 30 months: 77mmol/mol (p=0.35), 77mmol/mol (p=0.43) and 74mmol/mol (p=0.032), respectively. GLP-1 analogue introduction resulted in a significant decrease in body weight with most weight loss in the patients who had been on the treatment for the longest time (Table 1, Figure 3). At baseline, 6, 12, 18, 24 and 30 months the mean body weight was 104.9kg, 98.0kg (p<0.001), 98.5kg (p=0.0016), 94.7kg (p=0.00125), 96.2kg (p=0.0024) and 92.0kg (p=0.018). This was a percentage body weight reduction of: 6.6%, 6.1%, 9.7%, 8.3% and 12.2% at 6, 12, 18, 24 and 30 months, respectively (Table 1). Weight loss was not a significant confounder for decrease in HbA1c at six months (p=0.03) or 12 months (p<0.001); however, at 30 months the change in HbA1c was insignificant (p=0.32; Table 1). Due to small numbers, direct comparison between the different GLP-1 analogues was not performed.

When the cohort was split using BMI >35kg/m² as a cut off (BMI <34.9kg/m² [n=21], BMI >35kg/m² [n=12]), there was no significant difference in the change in HbA1c (p=0.75) between the two groups. There was no significant difference

### Table 1. Mean HbA1c, weight and weight change at follow-up intervals

<table>
<thead>
<tr>
<th>Variable</th>
<th>Months</th>
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<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean HbA1c, mmol/mol (with weight loss as covariant)</td>
<td>79</td>
<td>71</td>
<td>70</td>
<td>77</td>
<td>77</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>Mean weight, kg</td>
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<td>98.0</td>
<td>98.5</td>
<td>94.7</td>
<td>96.2</td>
<td>92.0</td>
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<tr>
<td>% weight change</td>
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<td>-6.1</td>
<td>-9.7</td>
<td>-8.3</td>
<td>-12.2</td>
<td></td>
</tr>
</tbody>
</table>

![Figure 2. Comparison in HbA1c between cohorts with BMI >35kg/m² and BMI <35kg/m² at each follow-up interval](image-url)
in weight reduction at any follow-up period between the two groups. However, at 30 months there was a noteworthy difference in weight change between the groups, with the lower BMI group achieving greater weight loss although this did not reach statistical significance. At baseline, 6, 12, 18, 24 and 30 months the difference in weight between the group with BMI <34.9 kg/m² and the group with BMI >35 kg/m² was: 99.6 vs 114 kg, 94.8 vs 105 kg, 95.4 vs 105 kg, 89.6 vs 105 kg, 91.9 vs 104 kg and 80.7 vs 115 kg. This was a percentage body weight reduction of 4.8 vs 7.6%, 4.3 vs 7.7%, 10.1 vs 7.9%, 7.7 vs 9.1% and 19 vs 0.5% at 6, 12, 18, 24 and 30 months between the group with BMI <34.9 kg/m² and the group with BMI >35 kg/m², respectively.

Data on changes to total insulin doses and C-peptide levels were not collected. There were no significant hypoglycaemic events reported nor evidence of metabolic decompensation during the study duration. No patient required unplanned hospital admission; in particular, there were no episodes of pancreatitis. No patients reported a pregnancy during the follow-up period.

Discussion
Adding a GLP-1 analogue to an established insulin regimen led to a sustained, statistically significant and clinically relevant weight loss in T1DM patients and also improved glycaemic control, with no evidence of metabolic decompensation. The improvement in glycaemic control was most notable at 12 months. The magnitude of weight loss was greater at six months than seen in the stage III clinical trials for GLP-1 analogues in T2DM. None of the trials in T2DM achieved a mean weight loss of more than 4 kg by six months, whereas we have demonstrated a mean weight loss of 6.9 kg at six months which continued to 12.9 kg (12.2% body weight reduction) at 30 months. Statistically, the degree of weight loss seen at 30 months was a confounding factor in the improved HbA₁c; however, this is still of clinical relevance. This improved response in T1DM with regard to weight loss may be associated with reduced insulin doses and a reduction in hypoglycaemia. Interestingly, the group of patients who had the best response in weight loss were those with BMI <35 kg/m².

In addition to significant weight loss, we demonstrated improved glycaemic control. In 2004, Dupré et al. demonstrated a 90% reduction of postprandial glucose rise and suppression of postprandial glucagon secretion with the addition of exendin-4 to insulin therapy in patients with T1DM. The question of whether the improved benefits obtained in terms of HbA₁c reduction are due solely to weight loss and improvement in insulin resistance, or due to a combination of this and reduced hyperglycaemia and reduced hepatic glucose production, is difficult to establish in this cohort. Recent animal studies demonstrate decreased expression of gastric GLP-1 receptors in T1DM, questioning previous consensus. This shows that the beneficial effects in T1DM remain unknown. In a study by Varanasi et al., liraglutide 0.6mg given to 14 patients for one week achieved a significant reduction in mean fasting glucose before any reduction in weight was seen. Other GLP-1 studies in T1DM are small and short term but provide proof of concept as all demonstrate significant weight loss with either reduction in the total dose of insulin or reduction in HbA₁c. The recent addition of the SGLT2 inhibitors to the armamentarium to treat the dysglycaemia in T2DM has led to early studies on the use of these medications as adjunctive therapies in T1DM also. The ATIRMA trial demonstrated benefit in terms of improvement in HbA₁c and reduction in hypoglycaemia and very early promise has
Intensive insulin therapy in type 1 diabetes can contribute to obesity and co-existent insulin resistance may increase the risk of complications. GLP-1 analogues have a potential role as an adjunct in type 1 diabetes for weight loss and improved glycaemic control. The mechanisms of reduction in postprandial hyperglycaemia, delayed gastric emptying and increased satiety are applicable in type 1 diabetes. We added a GLP-1 analogue to established treatment in 33 patients with type 1 diabetes. Results demonstrated clinically significant weight loss and a sustained improvement in glycaemic control. Benefits were seen from 6 months of treatment and persisted for the entire follow-up period of up to 30 months.

Key points
- Intensive insulin therapy in type 1 diabetes can contribute to obesity and co-existent insulin resistance may increase the risk of complications.
- GLP-1 analogues have a potential role as an adjunct in type 1 diabetes for weight loss and improved glycaemic control.
- The mechanisms of reduction in postprandial hyperglycaemia, delayed gastric emptying and increased satiety are applicable in type 1 diabetes.
- We added a GLP-1 analogue to established treatment in 33 patients with type 1 diabetes.
- Results demonstrated clinically significant weight loss and a sustained improvement in glycaemic control.
- Benefits were seen from 6 months of treatment and persisted for the entire follow-up period of up to 30 months.

been demonstrated by Kuhadiya et al. using triple therapy in T1DM combining intensive insulin with an SGLT2 inhibitor and a GLP analogue.25

Syed and Baldev have previously reported their experience of using the GLP-1 analogues in T1DM and subsequently developed a protocol agreed with their local clinical governance committee to ensure eligible patients are fully informed and properly consented before taking GLP-1 analogues. This seems a practical and sensible approach while GLP-1 analogues remain unlicensed in T1DM, in order to monitor the safety and efficacy of adjunctive therapy and to facilitate the process of regular clinical review.18

We have studied a larger number of patients for a longer follow-up period than has been reported previously; however, only eight patients so far have reached a follow-up duration of 30 months. The large drop in weight with reduction in HbA1c in this cohort suggests that treatment effect is prolonged and long-term therapy may remain beneficial. In view of the nature of this retrospective analysis we are unable to control for other factors impacting on glycaemic control and body weight in this cohort. This was not a case-control study and patients were selected from a large unit as being likely to benefit, meaning our results should be interpreted with caution due to selection bias. However, our population is typical of patients attending specialist diabetes services and our findings suggest that for selected patients this treatment is highly effective. We must also consider, however, the longer-term impact of these drugs as they remain a relatively new therapy in T2DM and long-term outcome and safety studies are not available. We must be cognisant that the T1DM cohort is younger and likely to be exposed to medications for a longer period. We also do not know what effect cessation of therapy will have on glycaemic control once target weight is achieved. It is imperative to counsel female patients about the lack of awareness of pregnancy outcomes using these and other adjunctive therapies, particularly as many pregnancies in the T1DM population are unplanned. The cost implication of adding GLP-1 analogues to insulin has not been studied. However, reducing complications by improving glycaemic control and reducing obesity are likely to offset cost of the medications, and importantly, are likely to lead to improved psychological wellbeing.

Conclusion
We have demonstrated that the addition of a GLP-1 analogue to existing treatment for a selected group of patients resulted in significantly improved glycaemic control and weight reduction in patients with type 1 diabetes.

Declaration of interests
There are no conflicts of interest declared.

References