The use of liraglutide, a GLP-1 agonist, in obese people with type 1 diabetes

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Abstract

Aims: **Optimisation of glycaemic control in type 1 diabetes often results in unwanted weight gain. glucagon-like peptide-1 (GLP-1) agonist use is associated with weight reduction in type 2 diabetes but its use in type 1 diabetes is little studied.**

Methods: **We developed a protocol for GLP-1 use in people with type 1 diabetes and obesity in which liraglutide was initiated and up-titrated whilst insulin doses were simultaneously titrated according to glycaemic parameters.**

Results: **Of 15 patients offered treatment, 8 proceeded. Baseline parameters were (n=8, mean ± SD): (age 50 ± 6 years, BMI 40.4 ± 5.5 kg/m^2, weight 123.0 ± 23.9 kg, HbA_{1c} 8.5 ± 1.7%, total daily insulin dose 131 ± 112 units/day. By intention to treat analysis (n=8, 12 months), at 3, 6 and 12 months compared to baseline, weight loss was 6.8 ± 4.1 kg, 10.0 ± 5.6 kg and 8.9 ± 8.4 kg (p=0.026). The reductions in insulin dosage were significant over 6 months (n=8, p=0.045) or when analysing only those who completed 12 months of liraglutide therapy (n=6, p=0.044).**

Conclusions: **GLP-1 agonist use in patients with type 1 diabetes may be advantageous where weight reduction becomes both a constraint and a therapeutic objective.**

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Key words: GLP-1, insulin, liraglutide, obese, type 1 diabetes, weight

Introduction

The management of type 1 diabetes is complex with multiple challenges. Optimisation of glycaemic control plays a key role in the prevention of both macro- and micro vascular complications[1] but often results in unwanted weight gain[2] and adverse clinical outcomes.[3] Even small reductions in weight significantly improve outcomes of obesity related chronic diseases.[4] Currently life style modifications are main stay treatment of obesity in type 1 diabetes. Whilst pharmacotherapy can augment the effect of life style modifications,[5] its role is limited such that bariatric surgery is often the only effective treatment for morbid obesity.[6] One of its subsidiary mechanisms may be increased production of GLP-1[7] since GLP-1 regulates appetite and satiety. That may be one reason, amongst many, why GLP-1 agonist use is associated with significant weight reduction in type 2 diabetes[8] and the non-diabetic obese population.[9,10] GLP-1 agonist use in type 1 diabetes is little studied either for the modification of glycaemic control or for weight. Preliminary evidence suggests liraglutide use in type 1 diabetes benefits glycaemic control, glucose variability, reduced dosage of insulin and body weight.[11-13] Based on this, we have developed and audited a local protocol for the use of liraglutide in obese patients with type 1 diabetes.

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Abbreviations and acronyms

ACR	albumin creatinine ratio
GLP-1	glucagon like peptide-1
BMI	body mass index
ELISA	enzyme-linked immunosorbent assay
HbA_{1c}	glycated haemoglobin

Methods

We developed a protocol for GLP-1 use in people with type 1 diabetes, obesity (BMI >35kg /m^2), progressive weight gain with or without constraint to insulin titration for better glycaemic control. The diagnosis of type 1 diabetes was according to standard clinical and biochemical parameters (acute onset, ketosis at presentation, insulin therapy from diagnosis and mandatory ongoing insulin need, C-peptide levels). Acceptance of patients onto the protocol required dual consultant specialist approval. After providing them with relevant information at consultation and in writing using a standardised information sheet, informed written agreement was obtained from all patients about the dual unlicensed use of liraglutide in type 1 diabetes and for the management of obesity. Liraglutide was initiated and up-titrated from 0.6 to 1.8mg over a 4–6 week period, whilst insulin doses were titrated according to glycaemic parameters. Patients had open access to support and follow up, and were minimally reviewed monthly. The key objectives were safe glycaemic control, weight loss of >5% at 6 months and GLP-1 agonist tolerability. Patients were reviewed for withdrawal at 3 months and withdrawn at 6 months if these were not attained. This protocol was agreed with local clinical governance committees, but since this was a service development and the presented data are an audit of the protocol, formal ethical committee approval was deemed not to be required. Statistical analysis was in SPSS version 21.

The non-parametric Freidman test for repeated, related measures was applied to test differences in parameters over time with $p<0.05$ taken as significant. Data are presented as the mean ± SD with the range.

Results

Over 1 year, of 15 patients offered treatment, 7 declined and 8 proceeded (age 50 ± 6 years, 4 females). One patient with BMI 30kg/m^2 was included due to rapid weight rise during insulin intensification such that the patient did not want to proceed without co-management of weight gain.

Summary results are presented in Table 1 and individual outcomes are shown in Figure 1.

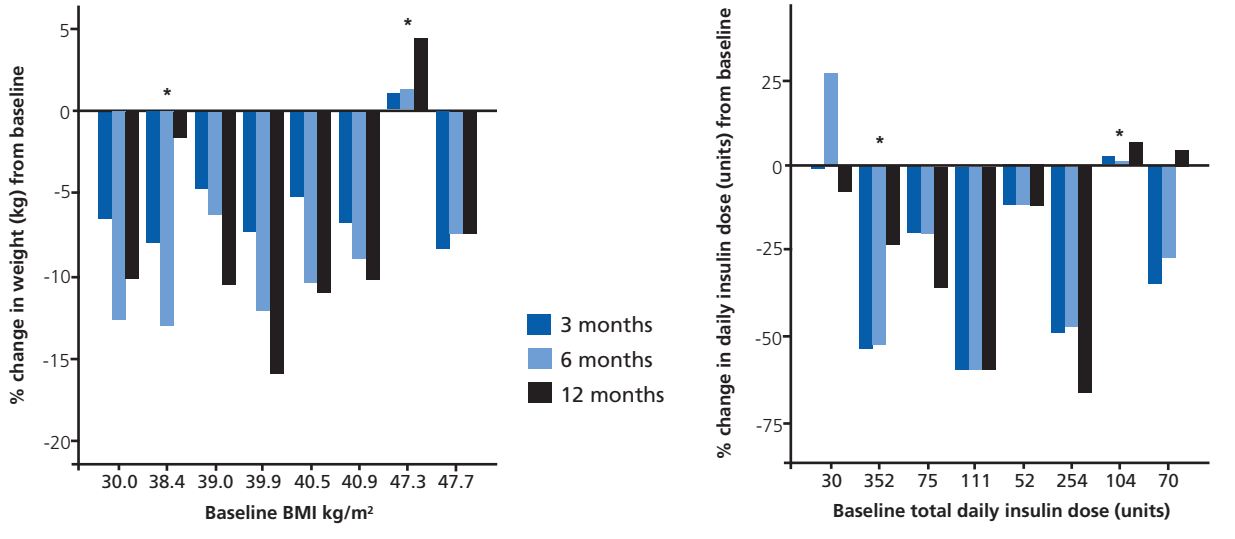
The baseline parameters were: BMI 40.4 ± 5.5 kg/m^2, (range 30-47.7 kg/m^2), weight 123.1 ± 23.9 kg (70.9-153.2 kg), HbA_{1C} 8.5 ± 1.7% (7.1-12.5%), total daily insulin dose 131 ± 112 units /day (30-352 units/day), creatinine 76 ± 21 µmol/L (53-110), ACR 1.5 ± 2.4 mg/mmol (0.3-7.5) , cholesterol 4.4 ± 0.8 mmol/L (3.2-5.5), C-peptide was negative (<94 pmol/l (analysed by the Mercodia C-peptide ELISA assay)) in 6 patients and low in 2 (281, 131 pmol/l), retinopathy status (none=1, background=2, pre proliferative and above=5), foot risk (low risk=5, intermediate risk=3) and only one patient had macrovascular complications.

On an intention to treat basis at 3, 6 and 12 months, weight loss was 6.8 ± 4.1 kg, 10.0 ± 5.6 kg and 9.0 ± 8.5 kg (range -21 to +6.8 kg) (p=0.026). Percentage weight loss at year end was 8 ± 6% (range +4 to -16%). Daily insulin dose fell by 52 ± 69 units, 50 ± 69 units and 43 ± 60 units (median 16, range -168 to +6 units) (p=0.107, ns). Insulin dosage in units/kg was 1.0 ± 0.9, 0.7 ± 0.4, 0.7 ± 0.4 and 0.7 ± 0.6 (p=0.136, ns). HbA_{1C} changes were

Table 1 Mean ± SD (range) of outcomes of HbA_{1C}, weight and insulin dosage over time in patients with type 1 diabetes treated with GLP-1 agonist therapy. P values are for the Friedman test for repeated measures over time. Significance is set at 0.05.

	Baseline	3 months	6 months	12 months	p value		
					6 months	12 months	
					n=8	n=8	n=6
HbA_{1C} (%)	8.5 ± 1.7 (7.1-12.5)	8.4 ± 1.3 (7.0-11.2)	8.0 ± 0.9 (6.7-8.7)	8.3 ± 1.6 (6.5-12.0)	0.497	0.771	0.409
Weight (kg)	123.0 ± 23.9 (70.9-153.2)	116.2 ± 24.5 (66.2-154.8)	113.0 ± 25.9 (62.0-155.0)	114.1 ± 26.4 (63.8-160.0)	0.021	0.026	0.003
Insulin dose (units/day)	131 ± 112 (30-352)	79 ± 49 (30-166)	81 ± 49 (38-168)	89 ± 78 (28-270)	0.045	0.107	0.044
Insulin dose (units/kg/day)	1.0 ± 0.9 (0.4-2.9)	0.7 ± 0.4 (0.4-1.5)	0.7 ± 0.4 (0.4-1.6)	0.8 ± 0.6 (0.4-2.3)	0.044	0.136	0.158

Figure 1. Percentage changes in weight (left panel) and total daily insulin dosage (right panel) over 3, 6 and 12 months compared to baseline in individual cases. Relevant individual baseline parameters are shown on the abscissa and are in ascending BMI order. Cases that withdrew at 6 months are denoted by an asterisk.



not significant (p=0.962, ns).

Two patients were unable to tolerate liraglutide and withdrew at 6 months. They are indicated in Figure 1. In one there was no response in any parameter (HbA_{1c}, weight or insulin dose), also mandating withdrawal. In the other, weight and insulin dosage rose following cessation of GLP-1 therapy. Excluding these two cases (n=6), insulin dose reduction over 1 year was significant (p =0.044) at 12 months (-44 ± 66 units per day) but with no significant difference when assessed by units/kg (p=0.158, ns). Percentage weight loss at year end was 11 ± 3% (range -7 to -16%, p=0.003).

Alternatively, analysis to the 6 month time point (n=8) showed significant falls in weight (p=0.021) and a significant reduction in insulin either by total daily dose (p=0.045) or in daily units/kg (p=0.044) whilst HbA_{1c} remained static.

There were no significant hypoglycaemic events nor any episodes of acute metabolic destabilisation.

Discussion

Under this tightly observed protocol, in motivated patients with type 1 diabetes, under close clinical supervision (and by whatever mechanisms of action[14-17]), significant weight reduction occurred without metabolic destabilisation. Clinically and statistically significant reductions in insulin dosages were achieved which appeared to be a consequence of the weight loss, possibly indicative of an improvement in insulin resistance as determined by the crude measure of the changes in units/kg. Perhaps disappointingly, attainment of glycaemia, did not improve. This at least allowed the true potential for weight loss to emerge independent of changes that might have resulted from sharp improvements or deteriorations in glycaemic control. The magnitude of weight loss in this group appeared to exceed that expected in type 2 diabetes,[18] possibly because of the interplay of GLP-1 effects together with the reduced pro-obesity effect of falling insulin dosage. It is possible that weight loss might not have been so good if we had simultaneously achieved a significant HbA_{1c} reduction, and it is known that intensification of insulin therapy to attain good control is associated with weight gain.[2] Interestingly, we observed a similar amplification effect when adding GLP-1 agonist therapy to those already on insulin therapy in type 2 diabetes.[19]

The individual variation of responses was of clinical importance. One patient had poor tolerability. Otherwise it can be seen that an effective response was clearly evident very early in the use of GLP-1 agonist therapy and, equally, non-responsiveness in a single patient was similarly obvious by 3 months.

Ethical issues around unlicensed uses of liraglutide in type 1 diabetes must focus on safety. Our preliminary experience is reassuring, but it is small scale and provides no more than a cautious "proof of concept" amongst the few other small-scale trials that have been published.[11-13, 20,21] There are no currently available data to suggest harm over and above the standard cautions and side effects understood and observed in mainstream clinical practice. Large, prospectively randomised studies have started to explore the role of liraglutide as additional treatment in type 1 diabetes.[22,23] Until they report, we would urge colleagues not to embark on this therapy without due regard to all local clinical governance processes, tight systems of clinical supervision, clear mechanism for independent peer review and a fully informed and consented patients, who have appropriate (and assessed and documented) levels of self-care proficiency.

We conclude that, under the appropriate conditions, and with appropriate patient selection, GLP-1 agonist therapy in type 1 diabetes may be advantageous where weight reduction becomes both a constraint and a therapeutic objective.

Key messages

In patients with type 1 diabetes and co-existent obesity, GLP-1 agonists;

- are currently unlicensed
- can potentially reduce body weight and reduce insulin requirements
- treatment requires close monitoring

Conflict of interest None.
Funding None.

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