The use of GLP-1 agonist therapy, liraglutide, is associated with significant weight loss in morbidly obese people without diabetes

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Abstract

Introduction: **In obesity, bariatric surgery is effective but carries morbidity and mortality risks. In type 2 diabetes, glucagon-like peptide-1 (GLP-1) agonist therapy results in weight reduction. Randomised controlled trials show efficacy in the non-diabetes obese population. Thus we have audited GLP-1 agonist use for weight reduction in morbidly obese people without diabetes.**

Methods: **A protocol for GLP-1 use in non-diabetes obesity (body mass index >35 kg/m^2) was agreed with local clinical governance committees. After liraglutide initiation, follow up was monthly, and the dose was up-titrated to a maximal 3 mg daily if indicated.**

Results: **Of 34 people offered treatment, 22 proceeded (age 42 ± 14 years, 17 females, 16 White Caucasians) and 14 completed 12 months of treatment. Absolute weight fell significantly from a baseline of 127 ± 19 kg (n=22) to 121 ± 19 kg (n=22), 119 ± 21 kg (n=21) and 110 ± 15 kg (n=14) kg at 3, 6 and 12 months respectively (all p<0.001 from baseline) amounting to -5.3 ± 4.4 kg, -7.4 ± 7.7 kg and -12.1± 9.6 kg at 3, 6 and 12 months respectively (all p<0.001 from baseline).**

Conclusions: **GLP-1 agonist therapy may play a significant role in people who have failed other weight loss options and are potential candidates for bariatric surgery.**

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Key words: morbid obesity, GLP-1 agonists

Abbreviations and acronyms

BMI	body mass index
GLP-1	glucagon-like peptide-1
GI	gastrointestinal
ITTB	intention to treat basis
NICE	National Institute for Health and Care Excellence
NHS	National Health Service
RCT	randomised clinical trial

Introduction

Obesity is a growing problem worldwide.[1] In the UK around a quarter of the population are obese.[2] Obesity, through different mechanisms, leads to several chronic diseases such as diabetes.[3]

Even small reductions in weight significantly improve the outcomes of obesity related chronic diseases.[4,5] Currently, lifestyle modifications are the mainstay treatment of obesity. Whilst pharmacotherapy can augment this effect,[6,7] its role is limited[8] due to the availability of only one drug and its side effects, such that bariatric surgery is often the only effective treatment for morbid obesity[9] but it has its own merits[10] and demerits.[11] Therefore, there is an increasing need to find other treatment options for weight loss that are effective and safe in this particular group of patients with significant risk.

GLP-1 agonist therapy, through the incretin effect,[12] can play a role in regulating satiety, feeding behaviour and body weight.[13] It is now a well-established treatment for type 2 diabetes where its weight loss potential is demonstrated.[14,15] One of the distinct features of GLP-1 agonist use is that it increases insulin secretion, while inhibiting glucagon, only in response to increases in glucose levels,[16,17] and so it can potentially be used in obese non-diabetic individuals without the risk of hypoglycaemia. There is now substantial RCT evidence that use of a GLP-1 agonist produces significant and sustained weight loss in non-diabetic obese people without causing any adverse effects on blood pressure, HbA_{1c} or lipid profile.[18-20]

In the UK, the use of GLP-1 agonists is not licensed for either the treatment of obesity or in people without diabetes. We present one year follow up of the use of the GLP-1 agonist liraglutide in practice outside the clinical setting amongst morbidly obese people without diabetes.

Methods

We developed a protocol for the use of GLP-1 agonist therapy in people with morbid obesity (BMI >35 kg/m^2) who have

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exhausted all other options for weight loss including intensive lifestyle measures and, in some cases, treatment with orlistat such that the only realistic option left for them was bariatric surgery, although they were not yet referred for it. Acceptance onto the protocol required dual consultant specialist approval. After providing patients with relevant information, both at consultation and in writing using a standardised information sheet, informed written agreement was obtained from all patients about the (United Kingdom) dual unlicensed use of liraglutide in people without diabetes and for the management of obesity. All people were at liberty, as with any intervention, to accept or decline this treatment option, based on available evidence, which was simply presented as another possible medical treatment for their obesity. Liraglutide was initiated and up-titrated from 0.6 to 1.8 mg over a 4–6 week period. The intention of progressing to a supra- maximal dose of 3 mg to maximise the weight loss[20] was based on a rolling clinical assessment tolerability and weight outcomes. Patients with effective and progressive weight loss were not up- titrated. Patients had open access to support and follow up as needed, and were minimally reviewed monthly.

The key objectives were safety and, in particular, no evidence of hypoglycaemia, acceptable GLP-1 agonist tolerability and weight loss amounting to >5% at 6 months. Patients understood they were to be reviewed for withdrawal at 3 months and were withdrawn at 6 months if weight loss was not attained. All patients had their weight, BMI and blood pressure measured at each visit and fasting blood glucose and cholesterol measured at baseline, 3, 6 and 12 months.

This protocol was agreed with local clinical governance committees governing out of license drug use, but since this was a development of our specialist obesity service and the presented data are an audit of an agreed protocol, formal ethical committee approval was deemed not to be required.

Statistical analysis was in SPSS version 22. 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.

An analysis on an ITTB was undertaken by carrying forwards the last known parameter estimation to the end point analysis in any patients who did not complete 1 year of therapy.

Results

In the first year a total of 34 eligible patients were offered the treatment of whom 22 wished to proceed and their demographic and baseline clinical parameters are shown in Table 1.

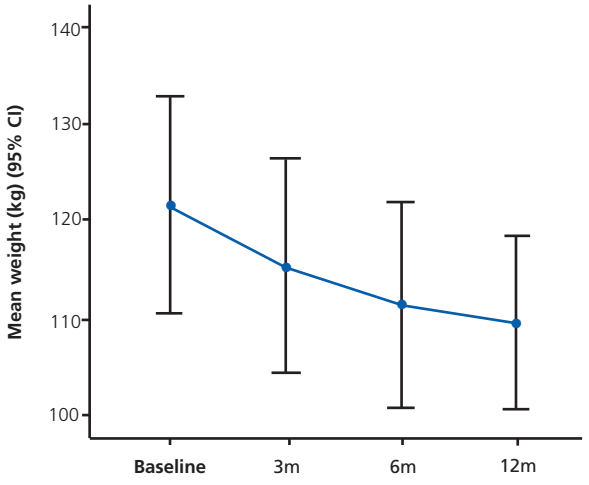
Their significant clinical comorbidities (range 1–12 per individual) were: respiratory problems including sleep apnoea (7), cardiac problems (7), poor mobility (5), mood disturbances (4), thyroid problems (7), polycystic ovarian syndrome (3), and other endocrine problems (3).

Of the 22 patients instigated on therapy, one dropped out after 3 months, a further seven at or after 6 months, leaving 14 who completed 12 months. Discontinuation occurred in two patients in whom there was no efficacy – indeed they gained weight – and otherwise the reasons for drop out were: GI side effects (2); withdrawal of primary care support to fund continued treatment (3); default (1).

Table 1 Demographic and baseline parameters presented as mean ± SD (range) or numbers with percentages

Age (years)	41 ± 12 (19-62)
Gender (female)	19 (86%)
Ethnicity (White Caucasian)	16 (73%)
Fasting blood glucose (mmol/l)	5.0 ± 0.6 (4.1-6.3)
Cholesterol / HDL ratio	4.1 ± 1.2 (3.1-7)
Systolic blood pressure (mmHg)	131 ± 21 (97-177)
Weight (kg)	127 ± 19 (95-171)
Body mass index (kg/m²)	45.8 ± 6.9 (36-59)

Figure 1. The group mean (with 95% CI) absolute weight at 3, 6 and 12 months



Only nine patients were escalated to the 3 mg dose at 3–6 months, this being dependent on drug tolerability and the rate of progressing weight loss.

Absolute weight fell significantly from a baseline of 127 ± 19 kg (n=22) to 121 ± 19 kg (n=22), 119 ± 21 kg (n=21) and 110 ± 15 kg (n=14) kg at 3, 6 and 12 months respectively (all $p<0.001$ from baseline), and this was also significant when analysed on the defined ITTB (n=22, 118 ± 20 kg at 12 months, $p<0.01$).

The magnitude of the weight loss was -5.3 ± 4.4 kg, -7.4 ± 7.7 kg and -12.1± 9.6 kg at 3, 6 and 12 months respectively (all $p<0.001$ from baseline) and -8.4 ± 9.6 kg in n=22 at 12 months

Figure 2. The group mean (with 95% CI) absolute weight change at 3, 6 and 12 months

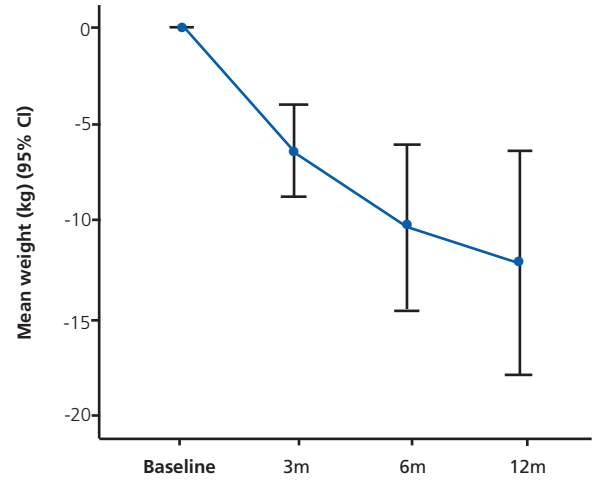
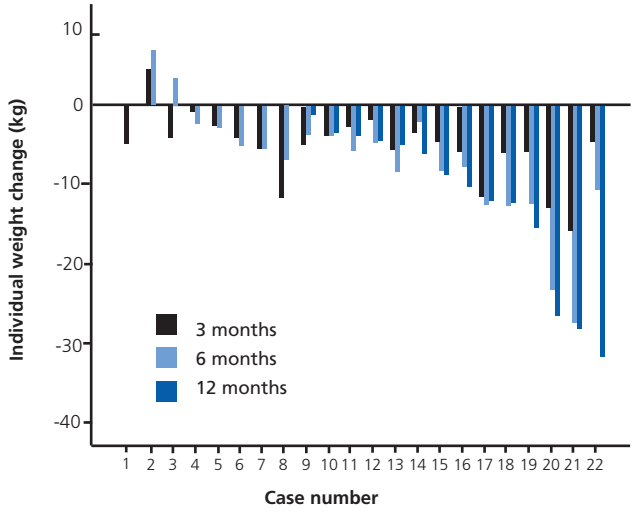


Figure 3. Individual weight change data at 3, 6 and 12 months (subjects are ordered by drop out point and then by magnitude of weight loss)



(p<0.001) on an ITTB.

At 12 months weight loss ranged from -1.1 to -31.7 kg (n=14) or +6.9 to -31.7 kg (n=22) on an ITTB (Figures 1–3).

Discussion

This group of non-diabetic patients with morbid obesity and co-morbidity were referred to us after the failure of all other intensified treatment modalities for the further management of their obesity including consideration for onward referral for bariatric surgery. Until the development of this protocol, we had very little to offer them. None of those who progressed with weight loss were subsequently referred and, of those who declined treatment or withdrew (n=20), four patients went on to be referred. Thus this treatment, if successful, might deflect surgical intervention.

Using the protocol, we have demonstrated that liraglutide use is practicable, safe and effective. The protocol we employed was a modification of those used in the several RCTs published to date,[18-20] with the escalation to a maximal 3 mg dose sequential and governed by tolerability and weight loss achievement. It is of note that, in this practical setting, of all patients qualifying for this protocol of care, one third declined after an informed discussion of the risk and benefits and another 40% dropped out during the year of observation, some due to lack of efficacy, some to intolerable GI side effects but more due to default and failure of external clinical support to the management plan. It is worth noting that amount of weight loss in our real life study was equivalent to the published RCT outcomes. The other distinguishing factor in our audit is that we demonstrate effective outcomes solely in those with morbid obesity whereas the RCT included patients with BMI as low as 27 kg/m^2.

In relationship to safety in this group of patients, our preliminary experience is very reassuring and much as expected by those who now commonly use GLP-1 agonist therapy in the diabetes population, but it is small in scale. However detailed safety data have been published[18-20] in large scale studies demonstrating no significant adverse events other than known GI side effects. Perhaps safety, and indeed efficacy, should rightly be considered around the only other available NHS option relevant to this group. In this context, bariatric surgery attains more weight loss than any non-surgical intervention,[21] although it has not been compared with GLP-1 agonist treatment, but this is at the expense of cost, mortality, morbidity and frequently adverse quality of life outcomes.[22-26] Noting that in some individual patients weight loss was >20 kg, it seems appropriate to call for quality RCTs to evaluate GLP-1 agonist therapy for weight loss against forms of bariatric surgery and, indeed, as a deflector for bariatric surgery in those who qualify under NICE guidance. Our conviction, based upon this experience, is that all patients destined for surgical intervention should be assessed for medical therapy with GLP-1 agonist therapy prior to proceeding.

To us, the only crucial question arising is how long should therapy continue in those with successful outcomes? RCTs have not published post-discontinuation data, but our intention is to continue so long as weight loss progresses or there is no weight gain at least to the 2 year time frame used in the study by Astrup *et al*.[27]

It is very difficult to understand why the RCT evidence to date[18-20] has not prompted the relevant NHS governing and commissioning authorities to undertake quality health and economic assessments. Unless this happens, such service provision cannot proceed and, on a negative note, our local commissioners, whilst accepting the clinical validity of the protocol and its clinical governance outcomes, ultimately declined to support primary care funding of the drug, leaving this to be either a matter for the hospital services and their budgets or to individual clinicians prepared to take individual prescribing responsibility. This was fully understood and accepted, since it is very inappropriate for local

Key messages

- Liraglutide produces significant weight loss in morbidly obese people without diabetes
- Once licensed, it could be a useful medical treatment option for obesity management

commissioners to have to decide on matters that are the domain of national organisations.

We conclude that, in a high risk population of those with morbid obesity and comorbidity, GLP-1 agonist therapy (liraglutide), used under a strictly governed process, is sufficiently effective to potentially deflect referral to bariatric surgery, thus avoiding significant cost, mortality and morbidity.

Conflict of interest None
Funding None

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