# The evolving world of GLP-1 agonist therapies for type 2 diabetes

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***Abstract*:** The glucagon-like peptide-1 (GLP-1) agonist drugs have attractions as a treatment for type 2 diabetes since they positively alter a number of key pathophysiological defects. These include increasing insulin release, reducing glucagon release, slowing gastric emptying and reducing food intake. In numerous clinical trials these agents have been shown to reduce DCCT-aligned $HbA_{1c}$ between 0.8% and 1.1% in patients with moderately controlled type 2 diabetes, whilst also being associated with some weight loss. Whilst medium-term safety and side-effect profiles are now well established, there are as yet no long-term studies on the safety of this group of drugs. The place of the GLP-1 agonists in the treatment paradigm for type 2 diabetes will evolve over the next decade.

***Keywords*:** exenatide, GLP-1, liraglutide, taspoglutide, type 2 diabetes mellitus, obesity

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## Introduction

In normal physiology the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) act to augment insulin release from pancreatic β cells. Both hormones are released by the gut after nutrient ingestion (GLP-1 from L cells in the distal gut, GIP from K cells in the upper small intestine) and appear in the peripheral circulation. Whilst both GLP-1 and GIP increase glucose-stimulated insulin release, metabolically they have some distinct differences in action. GLP-1 decreases glucagon release, inhibits gastric emptying, decreases appetite and reduces fat absorption from the gut. In contrast GIP increases gastrointestinal (GI) fatty acid absorption and increases lipogenesis in fat cells. Readers interested in the basic physiology and molecular biology of incretins should see Drucker [2006].

There has been an explosion in the variety of treatments available for treatment of type 2 diabetes mellitus over the last few decades; however, there has also been a parallel increase in scepticism over the safety of new drug treatments. Type 2 diabetes is a complex disease with multiple pathophysiological defects [DeFronzo, 2009] and the newer treatments have been specifically designed to take advantage of the increase in knowledge about these. The attraction of incretin-based treatments for type 2 diabetes is that they may have beneficial effects on a number of these key pathophysiological problems. GLP-1 agonists have been shown to increase insulin release, reduce glucagon release, delay gastric emptying and reduce food intake either by central and/or peripheral mechanisms. In contrast, interest in GIP as a potential treatment for type 2 diabetes waned quickly after it was found that it was ineffective in lowering blood glucose levels. This appears to occur due to a number of reasons including a lack of stimulation of late phase insulin release, a suppression of endogenous GLP-1 and a paradoxical increase in glucagon [Chia *et al.* 2009; Vilsbøll *et al.* 2002].

## Type 2 diabetes

Early exploratory studies in human subjects with type 2 diabetes showed that administration of GLP-1 to achieve near physiological levels was able to lower blood glucose concentrations [Toft-Nielsen *et al.* 1999; Rachman *et al.* 1997; Todd *et al.* 1997]. A medium-term subcutaneous infusion of GLP-1 over 6 weeks also showed sustained improvement in blood glucose levels without any tachyphylaxis [Zander *et al.* 2002]. The major difficulty in developing GLP-1-based pharmaceuticals has been the very short half-life of native GLP-1. In-vivo GLP-1 is rapidly inactivated in the blood stream by the neutral endopeptidase dipeptidyl peptidase IV (DPP IV), which cleaves peptides with a proline or alanine

residue at the second amino-terminal position. Early drug-development efforts were directed at developing GLP-1 agonist drugs that were resistant to degradation by DPP IV enzyme.

Two products with GLP-1 agonist activity are currently licensed for the treatment of type 2 diabetes and others are in development. Exenatide (synthetic exendin-4) is a DPP IV-resistant GLP-1 agonist with about 50% homology to native human GLP-1. Idiosyncratically it was discovered as a biological compound in lizard venom. Exenatide is resistant to DPP IV degradation by having a glycine residue at position 2. Liraglutide is a partially DPP IV-resistant analogue of human GLP-1 which contains an acyl fatty acid tail at amino acid 26. The fatty acid tail allows binding to endogenous albumin, hence restricting access to DPP IV enzyme and prolonging its absorption profile from subcutaneous injection sites.

A wide range of phase III trials have assessed the clinical effects of the two licensed GLP-1 agonists, usually in combination with other oral hypoglycaemic drugs (Table 1). All of these trials show clinically significant falls in blood glucose with $HbA_{1c}$ change in the range −0.8% to −1.1% over 6 months. There appears to be no major difference in glycaemia improvement in the different oral therapy combinations used, even when added to sulphonylureas. One commercially sponsored trial has compared the two GLP-1 agonist treatments to each other at the highest recommended doses (liraglutide 1.8 mg od, exenatide 10 µg bd). This suggested a slightly larger reduction in $HbA_{1c}$ with liraglutide −1.12% versus exenatide −0.79% [Buse *et al.* 2009]. Interestingly this study also suggested that exenatide lowered postprandial glucose excursion more than liraglutide, but fasting glucose was lower in the liraglutide treatment arm.

It must be remembered that phase III trials of GLP-1 agonists have included a concordant group of patients with moderately controlled diabetes with DCCT-aligned $HbA_{1c}$ usually in the range 7–10%. Patients with $HbA_{1c}$ above this range may not theoretically benefit well from this group of drugs since they are more likely to have a lower pancreatic insulin reserve for the incretin effect to work upon. Anecdotal reports exist from clinicians who have had dramatic results with patients with $HbA_{1c}$ values above 10%. It is not clear if this is due to an increase in concordance with treatment/diet therapy, the food restraint effect, lowering of glucagon or other factors.

Most published studies of this drug class have been of medium-term duration over 6 months. It is not yet clear whether the glucose lowering

**Table 1.** Summary of clinical trials using glucagon-like peptide-1 (GLP-1) analogues for the treatment of type 2 diabetes.

| Baseline treatment | Product | Comparator | Duration (weeks) | *n* | Δ $HbA_{1c}$ | Δ Weight (kg) | Reference |
|---|---|---|---|---|---|---|---|
| GLP-1 only | Liraglutide | Placebo | 14 | 42 | −1.4 | N/A | Vilsbøll *et al.* [2007] |
| GLP-1 only | Liraglutide | Glimepiride | 52 | 251 | −0.84 | −2.00 | Garber *et al.* [2009] |
| Metformin | Exenatide | Placebo | 30 | 113 | −0.80 | −2.80 | DeFronzo *et al.* [2005] |
| Metformin | Liraglutide | Glimepiride or placebo | 26 | 240 | −1.00 | −2.60 | Nauck *et al.* [2009a] |
| Metformin | Liraglutide | Sitagliptin | 26 | 225 | −1.24 | −2.86 | Pratley *et al.* [2010] |
| Metformin | Exenatide | None | 82 | 92 | −1.30 | −5.30* | Ratner *et al.* [2006] |
| SU | Exenatide | Placebo | 30 | 129 | −0.86 | −1.60 | Buse *et al.* [2004] |
| SU | Liraglutide | TZD or placebo | 26 | 228 | −1.10 | 0.30 | Marre *et al.* [2009] |
| TZD ± MF | Exenatide | Placebo | 16 | 121 | −0.89 | −1.75 | Zinman *et al.* [2007] |
| MF + TZD | Liraglutide | Placebo | 26 | 178 | −1.50 | −1.00 | Zinman *et al.* [2009] |
| MF + SU | Exenatide | Placebo | 30 | 241 | −0.80 | −1.60 | Kendall *et al.* [2005] |
| MF + SU | Liraglutide # | Glargine | 26 | 230 | −1.09 | −1.80 | Russell-Jones *et al.* [2009] |
| MF + SU | Exenatide | Glargine | 26 | 275 | −1.11 | −2.30 | Heine *et al.* [2005] |
| MF + SU | Exenatide | Novomix | 52 | 253 | −1.04 | −2.50 | Nauck *et al.* [2007] |

All doses of exenatide are 10 µg twice daily and liraglutide 1.2 mg daily unless otherwise stated. Weight loss quoted is against the baseline weight in the GLP-1 agonist treatment arm. *n* = number of subjects in the treatment arm of the study.
*Open-label extension study.
# Liraglutide dose 1.8 mg daily.
MF, metformin; SU, sulphonylurea; TZD, thiazolidinedione.

action is maintained over time. Two published studies have been of 1 year duration and suggest no major loss of glucose control in this time period [Garber *et al.* 2009; Nauck *et al.* 2007]. One study of exenatide lasting 82 weeks reports ongoing good glucose control, but it is an open-label extension study liable to confounding by responders staying in the trial [Ratner *et al.* 2006]. Of concern are the results of follow up of obese patients with type 2 diabetes treated by bariatric surgery. In the group of patients whose diabetes resolved soon after surgery ('diabetes remission') after 2 years 20% had developed diabetes again despite weight loss [Sjostrom *et al.* 2004]. This is relevant since the current best explanation for the fast resolution of diabetes after bariatric surgery is the postsurgical rise in gut-derived hormones including GLP-1 and peptide $YY_{3-36}$ (PYY) [Saliba *et al.* 2009; le Roux *et al.* 2006]. This would suggest that there may be a group for whom the durability of the clinical response in terms of blood glucose lowering is limited.

Clinically apparent side effects are mainly related to GI tract symptoms including nausea and vomiting. In one trial of exenatide 10 μg bd 48% subjects reported nausea and 13% vomiting [Kendall *et al.* 2005]. In clinical practice, however, it is surprising how infrequently GI tract side effects result in patient withdrawal from treatment. Drug-induced rash may also occur, with a frequency of less than 10%, but will usually necessitate withdrawal of treatment.

GLP-1 agonist drugs have a low propensity to cause major hypoglycaemia when used in combination with metformin and/or thiazolidinediones. Minor hypoglycaemia, however, does occur in 5–10% of patients. When used in combination with sulphonylureas prevalence of minor hypoglycaemia is higher and found in 15–30% of patients. In the head-to-head trial of exenatide and liraglutide minor hypoglycaemia was less frequent with liraglutide (26%) than exenatide (34%) [Buse *et al.* 2009]. Major hypoglycaemia has been reported in <1% of patients in most studies combining GLP-1 agonists with sulphonylureas, although one study using liraglutide reported a major hypoglycaemia prevalence of 2% [Russell-Jones *et al.* 2009]. Many clinicians will reduce the dose of sulphonylurea on initiation of these agents to reduce the possibility of major hypoglycaemia occurring. Driving licence authorities are currently monitoring the safety of this drug class in relation to motor vehicle accidents.

The long-term cardiovascular safety of GLP-1 agonist drugs is unknown as to date none of the trials have been sufficiently powered to assess cardiovascular mortality or cardiovascular events. Whilst it is hoped that the beneficial effects of this drug class on the cardiovascular risk factors of obesity, blood pressure and lipid profile would result in a favourable effect on cardiovascular disease, this thesis has yet to be proven. It is hoped that cardiovascular safety trials with these agents will be reported in the next 5 years.

## Weight change outcomes

A major reason that this drug class has generated so much interest is the fact that in clinical use GLP-1 agonists are associated with weight loss. This is the major distinction in comparison with other drug treatments for type 2 diabetes, which are either weight neutral or associated with weight gain. For patients considering a treatment for the first time, which requires self-medication by subcutaneous injection, the potential for weight loss may be an incentive. The degree of weight loss which occurs, however, is relatively modest. At 6 months of therapy, mean weight loss ranges from 1.6 to 2.8 kg (Table 1). The use of mean data, of course, hides the variability of weight change for individuals. Some patients experience no weight loss or even gain weight, whilst others experience weight loss of over 5 kg. In contrast, treatment of similar patient groups with insulin is usually associated with modest weight gain [Russell-Jones *et al.* 2009; Nauck *et al.* 2007; Heine *et al.* 2005]. Since this drug class is still relatively new it is still unclear whether the weight loss effect is either maintained or prolonged over a time period of greater than a year. The one study reporting weight change over a time period greater than a year is difficult to interpret as discussed above [Ratner *et al.* 2006]. Whilst this modest weight loss may have cosmetic and psychological benefits, it remains to be seen whether it translates into a clinically meaningful benefit in terms of cardiovascular health.

Weight loss is difficult to achieve in patients with type 2 diabetes. In studies of patients with obesity, but no diabetes [Astrup *et al.* 2009] or pre-diabetes [Rosenstock *et al.* 2010], using GLP-1 agonists with weight loss as the primary outcome measure, the mean weight loss was of the order of

5 kg at 6 months. The disparity in weight change between studies in nondiabetic subjects and type 2 diabetic subjects may relate to differences in the primary outcome measure (weight change versus blood sugar change) and a greater emphasis on the dietary intervention including a calorie deficit. One study combining lifestyle change with GLP-1 agonist therapy in patients with type 2 diabetes has shown a mean weight loss of 6 kg [Apovian *et al.* 2010]. This highlights that weight change as a variable in clinical studies is subject to numerous influences.

The requirement for injected treatment remains a major obstacle to many peptide therapies. Drug development in the arena of GLP-1 agonists has moved away from demonstrating a role for this drug class in treating type 2 diabetes to more user-friendly therapies. Two responses to this challenge have included the development of GLP-1 agonists with extended half-lives and small molecule agonists of GLP-1 receptors [Brubaker, 2010]. The rationale for extended half-life GLP-1 agonists is that they may reduce the incidence of undesirable GI side effects, but without a loss of clinical effects and reduce the frequency of injections. A number of long-acting GLP-1 agonists with dosing frequency of once weekly (or longer) are in the pipeline (Table 2). These compounds utilize different methods for extending the plasma half-life of the GLP-1 agonist beyond 12 hours including polymer microsphere technology (exenatide LAR or Bydureon®) and fusion to human albumin (albiglutide). Early indications suggest that these compounds have similar effectiveness in terms of blood glucose lowering compared to the commercially available GLP-1 agonists [Nauck *et al.* 2009b; Rosenstock *et al.* 2009; Kim *et al.* 2007].

Results from a number of phase III studies using taspoglutide will be announced during 2010. It should also be remembered that these compounds produce pharmacological elevation of GLP-1 levels that exceed the usual physiological range found in the postprandial state. Whether this will increase the likelihood of unwanted effects in the short or longer term is not yet clear.

## Areas of concern

Potential disbenefits of GLP-1 agonist drugs include uncertainty about their effect on risk of pancreatitis and various cancers. Concerns about an increased risk of pancreatitis arose after post-marketing surveillance of exenatide reported cases of pancreatitis [Ahmad and Swann, 2010]. This is a difficult topic in which to draw conclusions without large-scale studies due to the relative infrequency of acute pancreatitis in patients with type 2 diabetes: estimated at under 0.2% per year [Drucker *et al.* 2010]. Certainly patients with type 2 diabetes appear to be at increased risk of developing acute pancreatitis, perhaps related to obesity and hypertriglyceridaemia. At present the data would be best summarised as 'Not proven', but long term and large scale follow up studies are clearly desirable.

Another concern is the theoretical risk of increased cases of pancreatic carcinoma in subjects treated with GLP-1 agonists [Butler *et al.* 2010]. Increased cancer risk in patients with type 2 diabetes has come under closer scrutiny since the controversial series of articles linking insulin analogues to cancer risk [Smith and Gale, 2009]. Some animal model data suggest that GLP-1 agonists increase pancreatic duct replication, which is a potential risk factor for development of pancreatic adenocarcinoma. At present this will lead some clinicians to be conservative in the use of GLP-1 agonist drugs until more long-term data become available, whilst others may wish to counsel patients about the uncertainty in this area.

Concerns about medullary thyroid cancer (MTC) arose from toxicological studies in rodents in licensing studies for liraglutide.

**Table 2** GLP-1 agonist drugs licensed for type 2 diabetes or in phase III studies.

| Generic name | Trade name | Dosing schedule | Dose range | Company |
|---|---|---|---|---|
| Exenatide | Byetta | Twice daily | 5–10 μg | Lilly |
| Liraglutide | Victoza | Once daily | 0.6–1.8 mg | NovoNordisk |
| Exenatide LAR | Bydureon | Once weekly | 2 mg | Lilly/Amylin/Alkermes |
| Taspoglutide | N/A | Once weekly | 10–20 mg | Roche/Ipsen |
| Albiglutide | Syncria | Once weekly | 30 mg | GSK |
| Lixisenatide | N/A | Once daily | 10–20 μg | Sanofi-Aventis |

There certainly appear to be species differences between man and rodents in propensity to developing MTC. Rodents develop this tumour with a fairly high frequency, yet in man it is an uncommon tumour most often diagnosed in the context of multiple endocrine neoplasia syndrome (type 2) or with familial MTC. Rodent thyroid C cells have a cell surface GLP-1 receptor, whilst this does not appear to be the case for human thyroid C cells. Thyroid C cells secrete calcitonin, which is used clinically as a tumour marker for diagnosis and follow up of patients with MTC. Whilst liraglutide clearly stimulates secretion of calcitonin in rodents [Bjerre Knudsen *et al.* 2010], in humans liraglutide has not been shown to increase calcitonin secretion above the normal range [Parks and Rosebraugh, 2010]. Owing to the scarcity of this tumour in humans it will not be possible to find a signal for an increased risk in clinical trials of standard size, although a cancer registry has been set up. Although exenatide has not shown evidence of inducing C cell hyperplasia in rodents, this does not appear to be the case with exenatide LAR and may be a feature of all long-acting GLP-1 agonists [US Food and Drug Administration, 2010].

## Future clinical applications

Future uses of GLP-1 agonist therapies include combination with insulin(s). Whilst phase III trials conducted for drug-licensing purposes did not include cotreatment with insulin it has some attractions. Some obese diabetic patients are markedly insulin resistant, require large doses of insulin, but continue to gain weight and have poor diabetes control. Little has been published on the combination of insulin with GLP-1 agonist drugs, although anecdotally this has become established practice for some physicians. A retrospective study has suggested that adding exenatide to insulin therapy resulted in an improvement in blood glucose control whilst total daily dose of insulin reduced by 20% (mainly a reduction in prandial insulin doses) [Yoon *et al.* 2009]. In the UK a large nationwide voluntary audit of both exenatide and liraglutide is likely to release data on how common and effective this strategy may be in everyday clinical practice. Certainly one company has a patent on a drug formulation combining insulin and a GLP-1 analogue in fixed proportions.

Exploratory uses of GLP-1 analogues in clinical settings include intravenous infusion for inpatients [Sourij *et al.* 2009], as an adjunct to reduce post-prandial glycaemic excursions in patients with type 1 diabetes [Raman *et al.* 2010] and as a cytoprotective agent in subjects receiving islet cell transplants [Froud *et al.* 2008].

## Summary

GLP-1 agonist therapy has been available for the clinical treatment of type 2 diabetes for the last 5 years. As a drug class it has been welcomed as a new therapy group with the potential to treat diabesity. Optimism about improved cardiovascular risk profiles being translated into enhanced cardiovascular outcomes still abounds, but is not yet proven. Concerns about other potential long-term adverse effects remain unproven and will not be apparent for another 5–10 years. GLP-1 agonists have entered the therapy area for type 2 diabetes which is now rather crowded. There will be an interesting debate over the next decade over the optimum combination of drugs for type 2 diabetes. The players will be insulins, GLP-1 agonists, DPP IV inhibitors, thiazolidinediones and renal glucose absorption inhibitors.

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