Review Article

Advances in pharmacotherapy of Type-2 diabetes (Part-2: The incretin mimetics)

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Summary

Type-2 diabetes is witnessing major advances in pharmacotherapy. After a rather dormant period spanning the 1960s and the 1990’s following the discovery of the sulphonylureas and biguanide group of drugs, significant advances have been achieved in discovering new drugs. This would not have been possible if not for the advances in biotechnology. In this part of a series of reviews we shall be surfing the first group of the incretin based therapy, the incretin mimetics, exenatide and liraglutide. In a twin paper, the counterpart group of the incretin-based agents, the dipeptidyl peptidase inhibitors DDP-4 antagonists, the gliptins, will also be presented in details.

Keywords: Diabetes mellitus, Type-2 diabetes, Incretin based therapy, Incretin mimetics, Exenatide, Liraglutide, Metformin, Sulphonylureas

Introduction

In the previous article, we presented an overview of the conventional oral hypoglycaemic agents, metformin, sulphonylurea (SU), meglitinides, and thiazolidinediones (TZD), and their role in management of patients with Type-2 diabetes (Elhadd & Ahmed 2009)(1). In this review article, we discuss the mechanism of action, potential impact and the role of emerging incretin-based anti-diabetic therapies in management of patients with Type-2 diabetes, as well as a review of the latest clinical data in the field of incretin based therapy, focusing first on the incretin mimetics. Following this, a twin paper will cover the other component of the incretin based therapy, the DPP4 antagonists, the group also known as the gliptins. Subsequent issues, shall cover other therapies for Type-2 diabetes including insulin and other non-oral agents. We are also striving to present an overview of the advances in our understanding of the pathophysiology and genetics of Type-2 diabetes as well as emerging new therapies which are still in research pipelines.
**The incretin based therapy**

There had been previous experimentation in the early 20th century which was undertaken to elicit the chemical entities which stimulated the pancreas, and in 1932 J. La Barre was the first to propose the term incretin to describe the hypoglycaemia-inducing hormone(s) extracted from intestinal mucosa. Due to conflicting observations the incretin concept was discarded until the 1960s (2), when McIntyre noted that an intrajejunal glucose load almost doubled the insulin response to similar amount of glucose administered intravenously (3). These observations signaling the role of gastrointestinal processing in glucose homeostasis and in 1969 Unger & Eisenstrat (1969) coined the name of entero-insular axis to describe all gut hormones that influence insulin secretion (4). Later in 1979, Creutzfeldt was the first to suggest that this axis involve both humoral and neural factors (5). Gut hormones are well recognized to modulate glucose homeostasis. Gut hormones are normally secreted from the gut after glucose ingestion, and help regulate pancreatic hormones, insulin and glucagon, secretion, which in turn regulate hepatic glucose metabolism and modulate glucose homeostasis. These gut hormones were first hypothesized to exist when it was noted that ingested glucose elicits a larger and longer-lasting insulin response compared with intravenous glucose (3, 6). This is called incretin effect, which is defined as the ratio between insulin secretion during an oral glucose tolerance test and insulin secretion during an intravenous isoglycaemic glucose infusion (5). Two incretin hormones were later identified: GLP-1 (Glucagon-like peptide-1) and GIP (glucose-dependent insulinotropic peptide 1), and these hormones constitute more than 80% of the incretin effect. Levels of these hormones were shown to rise rapidly shortly after food intake, and then fall shortly thereafter as a result of rapid inactivation by the enzyme dipeptidyl peptidase-4 (DPP-4) (7). Of the two hormones, GLP-1 is secreted in greater concentration after nutrient ingestion, and is generally considered more physiologically relevant in human. The secretion of either of the incretin hormones depends mainly on the quality and quantity of food, with smaller and readily absorbable nutrients stimulates GIP and the converse is true for GLP-1 (7). Of the two incretin hormones, GLP-1 is secreted mainly from the entero-endocrine cells; L-cells; of the small intestine (mainly located in the lower part of small intestine). GLP-1 is produced through posttranslational processing of proglucagon gene. On the other hand, GIP secreted from another type of entero-endocrine cells, the K-cells which is situated in the upper part of the small intestine.

GLP-1 exerts wide array of actions involving an effect on pancreatic islets, as well as extrapancreatic effects involving actions on hepatocytes, adipocytes, skeletal muscles and central nervous system. In the pancreas it modulates glucose dependent insulin secretion and somatostatin secretion. It also leads to suppression of inappropriate glucagon secretion in the postprandial state. Peripherally it stimulates glucose uptake and disposal by skeletal and adipose tissues. GIP-1 also modulates glucose dependent insulin secretion, and stimulates glucose uptake and enhances growth, differentiation and neogenesis of the beta cells of the pancreas, and also delays gastric emptying and stimulates satiety centre (7).

Incretin effect is well documented to be impaired in patients with Type-2 diabetes with the primary defect lying at the level of β-cells (8), and there is impairment of GLP-1 secretion from L-cells, which is a major contributory factor (9). Impaired GLP-1 secretion in people with diabetes leads to...
defective glucose-stimulated insulin secretion, reduced glucose clearance and partly in quicker gastric emptying. One major mechanism of impaired incretin effect in Type-2 diabetes appears to be secondary to failure of glucagon suppression following glucose load\textsuperscript{[10]}. Initial evidence for the efficacy of supplementing incretin activity in patients with Type-2 diabetes came from short-term experiments in which exogenous native GLP-1 was administered by continuous IV or SC infusion. In these experiments, GLP-1 resulted in reduce blood glucose levels to near normal, restore post-meal insulin secretion and improves beta cell responsiveness to oral glucose\textsuperscript{[11]}. It is clear that the earlier experiments demonstrated that GLP-1 therapy is perfectly suitable for lowering blood glucose concentration in diabetes. However, because of its short half life (1–2 minutes) caused by rapid inactivation by DPP-4 enzyme and GLP-4, and being a peptide, which cannot be taken orally, these shortcomings may prohibit its long-term use for treatment of chronic condition, such as diabetes. It is also that continuous IV or SC infusion of GLP-1 is both expensive and impractical for the majority of people with diabetes. For these reasons research has focused on developing compounds that could either mimic the activities of GLP-1 while being less susceptible to DPP-4 inactivation, or ones which could limit the turnover of endogenous GLP-1 by inhibiting DPP-1 enzyme. Along these lines incretin-based therapies, incretin mimetics and DPP-4 inhibitor agents, have been developed. The incretin mimetics, such as exenatide and liraglutide, act by supplementing and/or replacing the activity of endogenous incretins and they have considerably longer half-life. While DPP-4 inhibitors represent the first oral agents aiming to increase endogenous incretin level and activity by inhibiting the DPP-4 enzyme.

1. GLP-1 agonists (Incretin-mimetics)

The first GLP-1 agonist to be developed is exenatide, whose parent compound was isolated from the saliva of the desert lizard, Gila monster (Heloderma suspectum). This synthetic GLP-1 agonist was developed and marketed by Eli Lilly, as exendine-4 (Exenatide, Byetta\textsuperscript{®}), and shares 53% homology with GLP-1 amino acid sequence, and binds avidly to the GLP-1 receptors, but is resistant to the action of DPP-1. As a result of this, exenatide has a greatly extended duration of insulinoineuric property compared to GLP-1, with a half-life of 2.4 hours compared to 2–3 minutes of that native GLP-1. Through its amino acid sequence homology with GLP-1, it is able to interact with GLP-1 receptors and to mimic all aspects of anti-diabetic activities of GLP-1. Thus, and as a result of stimulation of GLP-1 receptors, exenatide has been found to result in stimulation of the glucose-dependent insulin secretion, suppression of postprandial glucagon secretion, slowing of gastric emptying and reduction of food intake via promotion of satiety\textsuperscript{[12]}. Other actions include restoration of the first phase of insulin secretion and promotion of β-cells proliferation and islet cell neogenesis\textsuperscript{[13]}

Exenatide as an adjunct therapy to metformin or sulphonylurea (SU)

Exenatide has been studied extensively in human, and clinical and scientific studies provided evidence of the clinical efficacy and safety of adding exenatide to existing oral hypoglycaemic agents, metformin, sulphonylurea and thiazolidinedione (Table 1).
Table 1: Randomised studies of GLP-1 agonists (Exenatide and Liraglutide)

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Baseline HbA1c</th>
<th>Δ HbA1c vs. baseline</th>
<th>Δ Body weight vs. baseline</th>
<th>Common adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exenatide</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Added to metformin for 26 weeks</td>
<td>8.2%</td>
<td>0.8%</td>
<td>-3.0 kg</td>
<td>Nausea (45%)</td>
</tr>
<tr>
<td>Added to metformin for 30 Weeks</td>
<td>8.1%</td>
<td>1.3%</td>
<td>-3.0–5.3 kg</td>
<td>Nausea (14%)</td>
</tr>
<tr>
<td>Added to SU</td>
<td>8.6%</td>
<td>-0.9%</td>
<td>-1.6 kg</td>
<td>Nausea (51%) Hypoglycaemia (36%)</td>
</tr>
<tr>
<td>Added to metformin and SU</td>
<td>8.5%</td>
<td>0.8%</td>
<td>-1.6 kg</td>
<td>Nausea (49%) Hypoglycaemia (28%)</td>
</tr>
<tr>
<td>Added to TZD</td>
<td>7.9%</td>
<td>-0.9%</td>
<td>-1.7 kg</td>
<td>Nausea (40%) Vomiting (13%)</td>
</tr>
<tr>
<td><strong>Liraglutide</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monotherapy</td>
<td>8.5%</td>
<td>-1.4%</td>
<td>-3 kg</td>
<td>Nausea (7.3%) Diarrhoea (21%)</td>
</tr>
<tr>
<td>Added to metformin</td>
<td>9.5%</td>
<td>-1.0%</td>
<td>-2.2kg</td>
<td>Nausea (35%)</td>
</tr>
<tr>
<td>Added to SU</td>
<td>8.4%</td>
<td>-1.1%</td>
<td>-1.8kg</td>
<td>Hypoglycaemia (10%), Nausea (8%) Vomiting (5%)</td>
</tr>
</tbody>
</table>

Three 30-week, placebo-controlled trials enrolling 1446 patients have been conducted to evaluate the safety and efficacy of exenatide in patients with Type-2 diabetes whose glycaemic control was inadequate with maximally effective dose of metformin alone (n=336 patients), a sulphonylurea alone (n=377 patients), or a combination of sulphonylurea and metformin (n=733 patients). Patients were randomized to receive either exenatide (5mcg or 10mcg) or placebo for 30 weeks whilst continuing their existing oral hypoglycaemic agents. The primary end point for all these trials was glycaemic control as assessed by HbA1c. Regardless of the existing oral anti-diabetic agent therapy, exenatide has been shown to result in significant but modest incremental reduction in HbA1c(14,15,16). Combination with metformin results in a reduction of HbA1c of 0.4%-0.8% together with an added benefit of weight reduction of average of 3 kg(14), while addition of exenatide to SU resulted of average reduction of HbA1c of 0.5-0.9% with the exenatide dosage of 5 mcg & 10 mcg respectively(15). In the group where exenatide was added to the combination of SU and MF the reduction of HbA1c was 0.6-0.8% respectively for the dose of exenatide used, and weight reduction was an average of 1.6 kg(16). Fasting blood glucose was reduced in all these studies.

In the above trials, and on an intention to treat (ITT) basis, significantly more of those patients with an HbA1c > 7% at baseline who received exenatide 10 micrograms in addition to their existing therapy achieved an HbA1c ≤ 7% at 30 weeks: 40% compared to only 11% of patients on metformin alone, p<0.01(14), 34% of patients on exenatide compared to 8% on sulphonylurea alone, p<0.0001(15) and 30% of patient on exenatide compared to 7% on metformin-sulphonylurea combination therapy alone, p<0.0001(16).

In an open labeled long-term 52-week extension study of the exenatide and metforin study by Kendall et al(14), which involved 314 patients, of whom 57% completed full 82 weeks, the report indicates that long-term exenatide therapy provides incremental reduction of HbA1c of up to 1.3%, when combined with metformin and up to 1.1% in overweight patients and 48% of patients achieved HbA1c <7.0% at the end of the study(17).
The most common adverse effects with exenatide therapy observed on the above clinical trials (13-17) were gastrointestinal, with nausea been the most common adverse effect occurring in one third to half of exenatide treated patients, but vomiting and diarrhoea were less common (12-17%). Although these side effects are common, the frequency and severity decrease as treatment continued. The incidence of mild to moderate hypoglycaemia was less common when exenatide was used as monotherapy (5%). However, when used in combination with other anti-diabetic agents the incidence of mild to moderate hypoglycaemia increases from 5% with metformin to up to 36% with sulphonylurea. Thus, when combining exenatide with sulphonylurea, a reduction in sulphonylurea dose should be considered.

Long-acting release formulation of exenatide (exenatide LAR), which consist of microspheres containing exenatide and a polymeric matrix, has been investigated in phase 2 and 3 trials. Although data are limited, however current evidence indicates that exenatide LAR is both effective and safe(18,19). In a 15-week trial comparing the effect of exenatide LAR with placebo in patients with suboptimal blood glucose control despite diet, exercise and metformin(18). In a 15-week trial comparing the effect of exenatide LAR with placebo in patients with suboptimal blood glucose control despite diet, exercise and metformin(18). In this trial, exenatide LAR resulted in significant reduction of HbA1c of -1.7% and improvement of fasting blood glucose levels. A second trial compared the effect of exenatide LAR on blood glucose control with that of exenatide twice daily. At the end of 30-week, HbA1c decreased by -1.9% in exenatide LAR treated patients, compared to 1.5% in patients receiving exenatide twice daily(19).

Can we use incretin-mimetic as monotherapy rather than an adjunct therapy?

There are some preliminary evidence to suggest that monotherapy with exenatide in solo may be more effective than exenatide in a combination with oral antidiabetic agents. Nelson et al (2007) conducted a randomized double-blind trial comparing the use of exenatide 10mcg with placebo, followed by an open label arm of exenatide alone or exenatide with metformin(20). The study reported that exenatide 10 mcg twice daily as monotherapy was more effective than placebo in achieving the study endpoints (HbA1c & fasting blood glucose). On the other hand, exenatide was as equally effective as monotherapy compared to exenatide with metformin.

Thiazolidinediones (TZD, glitazones) and incretin mimetics

The concept of combining incretin-mimetics or DDP-4 inhibitors to TZD in patients with Type-2 diabetes is appealing from pathophysiological perspective. Glitazones act on insulin resistance and the incretin-mimetics/DDP-4 target the other facets of metabolic defects of Type-2 diabetes, namely the abnormalities of defective insulin secretion and inappropriate glucagon secretion(21). Zinman et al (2007) conducted a short term study of 16 weeks duration in Type-2 patients who were sub-optimally controlled with thiazolidinedione with or without metformin(22). Patients were randomized to receive exenatide or placebo in a double blind manner. A change in HbA1c from baseline was the primary endpoint and changes in fasting blood glucose, body weight, and hypoglycemia and GI side effects were the secondary endpoints. Exenatide had significantly reduced HbA1c, body weight and fasting blood glucose levels. Gastrointestinal side effects were relatively high (40%). The major limitations of the study are the shorter duration of the study and SU was not assessed in the study.
Which is more effective as an add on therapy, exenatide or a glitazone (TZD)?

This has been systematically reviewed. In a meta-analysis by Pinelli et al (2008)\(^{(23)}\), who evaluated the efficacy and safety of adding exenatide or thiazolidinedione (glitazone) to other oral antidiabetic agents, The outcome of 22 publications with 24-month duration or more, with collective endpoints of HbA\(_{1c}\) reduction, proportion of subjects reaching target HbA\(_{1c}\) of <7\%, mean changes in fasting plasma glucose, body weight, and finally the occurrence of severe hypoglycaemia, and gastrointestinal side effects. Both agents were efficacious in improving blood glucose control, but TZD resulted in greater reduction in HbA\(_{1c}\) (-0.8\%) than exenatide (-0.6\%), albeit at the expense of more weight gain, whereas exenatide failed to achieve a decrease in fasting plasma glucose, but with the advantage of weight loss. Both agents were not associated with increase in the incidence of mild or moderate hypoglycemia, though more gastrointestinal side effects in form of nausea, vomiting and diarrhoea were common in the exenatide groups, than those on TZD. To summarize, incretin mimetics could be a useful in combination with TZD rather than a substitute for TZD as the current evidence does not support a superior effect of TZD over these new agents.

**Use of exenatide with insulin**

The effect of exenatide on blood glucose control and body weight were compared with that of insulin glargine in a 26-week, open-label, controlled randomised study\(^{(24,25)}\). In these studies, patients who enrolled in the study continued their prior regime with metformin and sulphonylurea, but then they were randomly assigned to receive additional treatment with either exenatide or insulin glargine. Both exenatide and insulin glargine has equally improved blood glucose control, with no difference in HbA\(_{1c}\) (-1.25\% and -1.26\% respectively). Exenatide reduced postprandial glucose excursions more than insulin glargine, while insulin glargine reduced fasting blood glucose levels more than exenatide. Body weight decreased 2.3 kg with exenatide and increased 1.8 kg with insulin glargine (difference, -4.1 kg [CI, -4.6 to -3.5 kg]. Rates of symptomatic hypoglycaemia were similar, but nocturnal hypoglycaemia occurred less frequently with exenatide. The use of exenatide in insulin-treated Type-2 diabetic patients was explored by several investigators. A retrospective study by Viswanathan et al (2007)\(^{(26)}\) examined the addition of exenatide to a group of 52 subjects with Type-2 diabetes who were on insulin plus OHA\(^{(26)}\). There was no significant improvement in HbA\(_{1c}\), but the reduction in weight and in total insulin daily requirement was significantly different after 26 weeks of therapy. However, there was high drop out rate in this study. In another prospective study, Govindan et al (2008) studied patients with insulin treated diabetes who failed to achieve the HbA\(_{1c}\) target, and who also have problem with progressive weight gain\(^{(27)}\). At the end of the study, there was no improvement in HbA\(_{1c}\), but there was significant reduction on the total daily insulin, and patients managed to lose weight. Of interest, 10 of the 24 patients in this study were able to stop insulin completely. Further, the incidence of severe hypoglycaemia was not increased. In a retrospective study involving 134 insulin treated patients, the effect of addition of exenatide to insulin therapy was assessed after a mean follow up of 15-month. The improvement in HbA\(_{1c}\) was significant compared with baseline, and on average there was a weight loss of 6 kg (72\% of study subjects lost weight)\(^{(28)}\). Furthermore, 22\% of the study patients were on SU therapy at the outset of the study, and at the
end of the study this dropped to only 9%. The use of glitazones, metformin and meglitinides did not change significantly, nor was there a significant reduction in the total daily dose of insulin. Mild GI side effects was common, though mild (occurred in 42%), and 7 patients dropped out of study because of side effects. Only one patient in this study had severe hypoglycaemia requiring hospital admission. The study by Davis et al (2007) has suggested that patients with Type-2 diabetes who has longer diabetes duration, and those who are taking higher doses of insulin therapy may experience deterioration of their control if they substitute exenatide for insulin(29). In a review of phase-III human clinical trials and post hoc completer analysis exenatide therapy was confirmed to achieve similar improvement in glycaemic control to that achieved by once daily insulin glargine or twice daily isophane insulin(30). The observed side effect profile mainly of mild to moderate nausea and rates of hypoglycemia were comparable to that of placebo (when combined with metformin) and to insulin comparator (when combined with metformin & SU). In the same analysis, the use of exenatide with metformin or SU was associated with significant improvement of health related quality of life (HR-QOL). Furthermore, cost-effectiveness analysis also showed that exenatide is comparable to insulin glargine, glibenclamide and pioglitazone when combined with metformin. In a post hoc analysis of pooled data from two other studies, the use of exenatide was compared with insulin analogues (either insulin glargine or biphasic insulin as part) with changes in weight as the main endpoint. The use of exenatide over 6 month period was associated with an average weight loss of 3 kg while the converse was true for insulin analogue subject users who gained on average 3 kg(31).

To summarize, the incretin mimetics, exenatide, may prove to be an attractive agent to be used in insulin treated Type-2 diabetic patients who are not achieving the adequate blood glucose control. Benefits include in addition to perceived improved glycaemic control, favourable impact on weight (which is the usual conundrum in these patients whose weight tend to increase following insulin therapy). Also the potential of significant reduction in total insulin daily requirement and the prospect of stopping insulin all together are other benefits, but the preliminary evidence suggests that this may be confined to patients who have residual beta cell function.

**Liraglutide**

The second GLP-1 mimetic, liraglutide, is a human GLP-1 analogue and is produced by recombinant DNA technology in Saccharomyces cerevisiae. Liraglutide is nearly identical to native human GLP-1, with only a single amino acid substitution, and has 97% homology with GLP-1 amino acids sequence. Liraglutide is produced as a result of substitution of Lys34 with Arg34, and an attachment of a C-16 free-fatty acid derivative via a glutamyl spacer to Lys26(32). The free fatty acid derivative is thought to promote non-covalent binding of liraglutide to albumin, therefore, increasing plasma half-life through protection from renal clearance, limiting metabolism by DPP-4, and slow absorption rate from injection site. Like exenatide, liraglutide needs to be injected subcutaneously. After SC injection, its maximum plasma concentration is reached after 10– 4 hours, and its half-life is 11– 3 hours(33, 34).

The efficacy and safety of liraglutide in patients with Type-2 diabetes was assessed in Liraglutide Effect and Action in Diabetes (LEAD) programme, a series of randomised, controlled, parallel-group(35-40) (Table 1),
multi-centre studies in which liraglutide was compared to placebo and/or a specific comparators anti-diabetic agent in varying combinations. Active comparators included rosiglitazone, glimepride, insulin glargine or exenatide. In these studies, liraglutide was assessed as adjuvant dual therapy in combination with metformin, glimepride or another sulphonylurea, or liraglutide was assessed in triple adjuvant therapy in combination with metformin and rosiglitazone, metformin and glimepride and metformin and another sulphonylurea. In the last LEAD 6 study liraglutide was compared with the other GLP-1 agonist, exenatide in patients with Type-2 diabetes in combination with metformin and sulphonylurea. The duration of each LEAD studies range from 26-52 weeks, and recruited patients aged 18–80 years with Type-2 diabetes who were treated with oral anti-diabetic agents as monotherapy or combination treatment for at least 13 weeks. The baseline HbA1c of these patients was 7.0–1.0%. The primary endpoint was the change in HbA1c from baseline after 26 weeks of treatment. The secondary endpoints of these studies included change in body weight, systolic blood pressure and proportion of patients achieving an HbA1c ≤6.5%.

In LEAD 1 study\(^{(35)}\), patients were randomised to treatment with placebo, rosiglitazone or liraglutide. All patients were taking glimepride in addition to the study medication, placebo, rosiglitazone or liraglutide. Liraglutide in combination with glimepride provides statistically significant improvement in blood glucose control compared to rosiglitazone and glimepride. HbA1c was reduced 0.4% in the rosiglitazone plus glimepride group compared with 1.1% in liraglutide plus glimepride group. Liraglutide resulted in better fasting and post-prandial blood glucose levels, and there were significant weight difference as liraglutide resulted in 1.8 kg weight reduction. It should be noted that the dose of the active comparator rosiglitazone (4 mg) in this dual therapy study was lower than normal clinical use, and therefore, is not the most appropriate of comparisons. In LEAD 2 study\(^{(36)}\), and after 4 week run-in period to reach the maximum dose of metformin, patients were randomised to treatment with placebo, glimepride or liraglutide. Thus in LEAD 1 and 2 studies liraglutide was added to anti-diabetic monotherapy or substitution of one of the anti-diabetic agent. In LEAD 2 study, liraglutide plus metformin resulted in significant reduction of HbA1c of 1.0% after 26 weeks. This HbA1c reduction with liraglutide plus metformin was comparable to that HbA1c reduction with glimepride plus metformin, but significantly greater than the HbA1c increase of 0.1% observed with placebo plus metformin. However, there is significant weight loss, less hypoglycaemia with liraglutide, but more nausea. The long-term efficacy of liraglutide was demonstrated in 52-week LEAD 3 monotherapy trial\(^{(37)}\). In this study, 746 patients were randomised to treatment with liraglutide 1.2 mg or 1.8 mg vs. glimepride 8 mg. These patients were not taking any other anti-diabetic agent and both liraglutide and glimepride were given once daily. In this study, liraglutide 1.2 mg and 1.8 mg decreased HbA1c by 0.8% and 1.1% respectively compared to 0.5% reduction of A1c with glimepride. Liraglutide also resulted in significant improvement in fasting as well as post-prandial blood glucose levels compared to glimepride, and more weight loss, less hypoglycaemia, but more nausea with liraglutide treatment. Zinman and colleagues reported the results of LEAD 4 study\(^{(38)}\). The addition of liraglutide 1.2 mg and 1.8 mg to patients
concomitantly receiving metformin and rosiglitazone resulted in a 1.5% reduction of HbA1c, improvement in fasting and post-prandial glucose and reduction in body weight. The changes in blood pressure with liraglutide treatment were most notable in this study, with a decrease in systolic blood pressure of 6.7, 5.6 and 1.1 mmHg with 1.2, 1.8 mg liraglutide and placebo respectively. In LEAD 5 study, the efficacy and safety of liraglutide were compared to insulin glargine therapy and placebo(39). Patients with Type-2 diabetes who were taking metformin plus glimepride were randomised to treatment with liraglutide 1.8 mg, placebo or insulin glargine administered once daily(39). Liraglutide produced significant reduction in HbA1c compared to placebo or insulin glargine (-1.33, -0.2 and -1.1% respectively). Significantly, more patients achieved HbA1c of ≤6.5% with liraglutide than with placebo or insulin glargine. There were significant decrease in body weight and systolic BP in the liraglutide arm (1.8 kg and 4 mmHg respectively) versus insulin glargine arm where body weight and systolic BP increased.

Liraglutide has also been compared with exenatide as add-on therapy in a 26-week LEAD 6 trial involving 464 patients with Type-2 diabetes treated with maximally tolerated dose of metformin, sulphonylurea or both(40). The patients were randomised to treatment with either liraglutide 1.8 mg once daily or exenatide 10 mcg twice daily for 26 weeks. HbA1c, a key measure of glycaemic control, was reduced by 1.12% with liraglutide, which was significantly greater than the reduction with exenatide (0.79%). Moreover, more patients taking liraglutide reached target HbA1c level of ≤7.0% (54% vs 43% respectively). Fasting blood glucose level improved with both treatment, however; lower level was achieved with liraglutide compared to exenatide. Mean weight loss was similar for both treatment (3.24 vs 2.87 kg respectively). Liraglutide monotherapy was also evaluated in patients who did not achieve glycaemic control despite treatment with oral antidiabetic agents(41). These patients were either on diet with HbA1c 7.5% to 10% or on oral antidiabetic monotherapy with HbA1c 7.0–9.5%. Liraglutide monotherapy was associated with HbA1c reduction of 1.74% compared with placebo after 14 weeks of treatment. Liraglutide treatment was associated with significant improvement in fasting blood glucose and weight loss of up to 3 kg at the end of the study compared to placebo. Most frequently reported adverse events associated with liraglutide treatment were nausea and vomiting, especially at higher doses(35-40). Hypoglycaemia occurred in 8% of patients with liraglutide monotherapy, and 24% of glimepride plus liraglutide treated patients. Minor hypoglycaemia occurred in fewer than 4% of liraglutide patients compared with 3% of metformin patients. The combination of liraglutide with metformin plus glimepride resulted in minor hypoglycaemia in 27% compared with 17% of those treated with metformin and glimepride, and 29% for combination of insulin glargine metformin plus glimepride. Liraglutide therapy has demonstrated considerable clinical efficacy and safety in the above clinical trials, LEAD programme, and liraglutide treatment has been shown to lead to reduction in A1 HbA1c, fasting as well as postprandial blood glucose levels, and weight loss, with no significant adverse events profile.

Beyond glycaemic control and weight effect
Beyond their effects on glycaemic control and body weight, both exenatide and liraglutide have demonstrated additional novel features including their positive effects on β-cells, as well as an improvement
in lipid profile and systolic blood pressure. The current evidence demonstrated that incretin mimetics improve some parameters of β-cell function during treatment. Although β-cell function cannot be measured directly in human subjects, indices of beta cell mass and function can be estimated indirectly by assessing some marker such as Homeostasis Model of Assessment: Beta-cell function (HOMA-B), the proinsulin:insulin ratio, the arginine stimulated C-peptide. Exenatide treatment has been shown to improve β-cell function, and HOMA-B value increased from baseline by 32% in exenatide treated patients following 24 weeks treatment compared to only 6% for placebo (p=0.02)(42). Following one year treatment with exenatide, the arginine stimulated C-peptide test showed a 2.19-fold increase from baseline in beta-cell function compared to only 0.3-fold increase in function for exenatide (p<0.0001)(43). After 30 weeks of exenatide therapy, insulin secretion rate were shown to increase by up to 72%. Liraglutide, however, has also shown an increase in beta-cell function in patients with Type-2 diabetes. The addition of liraglutide 1.8 mg to metformin, glimepiride or combination for 26 weeks resulted in 28% to 34% improvement in beta-cell function(35,40). Liraglutide has shown to increase first phase insulin secretion by up to 114%. Whether the improvement in beta cell function observed in clinical studies are the direct effects of GLP-1 agonist on beta-cell function or is a result of improved blood glucose control remains to be elucidated. A lasting effect of incretin mimetics on beta-cell function however has not been demonstrated after washout period following one year treatment with exenatide. This may indicate a potential halt in progression of beta cell improvement following discontinuation of treatment, this however need to be further investigated to make firm conclusion.

Studies have suggested cardio-protective activities of GLP-1 agonists, however long-term studies to prove cardiovascular benefit are necessary in order to make firm conclusion on that. Current evidence has shown positive effects of exenatide and liraglutide on surrogate cardiovascular parameters such as systolic blood pressure, triglycerides, endothelial function and brain natriuretic peptide. Exenatide studies have demonstrated a marked improvement of lipid profile with exenatide therapy, with substantial reduction in apolipoprotein B (ApoB) (-5.2 mg/dl), triglycerides (-7.3 mg/dl), and an increase in high density lipoprotein cholesterol (+4.5 mg/dl), together with small reduction in total cholesterol and low density lipoprotein cholesterol(17). In addition, exenatide appear to be associated with substantial improvement in systolic blood pressure(17). This improvement of lipid profile and blood pressure may be partly related to weight loss experienced with exenatide therapy. The studies of liraglutide have also shown substantial reduction in triglyceride of 22%, and a reduction of blood pressure of about 7.9 mmHg(41). The reduction of triglyceride and systolic blood pressure after a short period of liraglutide treatment suggests that GLP-1 has direct effect on triglyceride and blood pressure which is possibly not simply the result of weight loss.

In conclusion, the incretin mimetics, exenatide and liraglutide, appear to be promising agents to help in the management of patients with Type-2 diabetes. Perhaps, the most significant beneficial effect of incretin mimetic agents is the glucose dependent insulin secretion, which probably mimics the physiological post-prandial insulin profile, and is associated with low rate of hypoglycaemia. In addition to this,
and probably more significant to most of type 2 diabetic patients, these agents will not lead to weight gain, and in fact provoke significant weight loss. Additional novel features include the positive effect on beta-cell function and improved cardioprotective activities. Their main disadvantage is that they are not oral agents. However; they hold great potential to tackle the long lasting issue of secondary failure to oral antidiabetic agents. Their effects on some of the core pathophysiological defects, and the preliminary evidence of their positive effect on beta cell mass and function holds great promise. They appear to be an attractive combination with all the existing oral agents, and their use with glitazone (TZD) and insulin may hold specific advantages. Furthermore, the long-acting form of exenatide would be a real breakthrough in this area, as a one weekly injection will greatly boost the compliance of those patients with diabetes.

References
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