Expert Opinion

1. Introduction

Diabetes mellitus (DM) affects 150 million adults and is one of the leading causes of mortality in the world [1]. Although a number of compounds are used for diabetes treatment, these are not suitable for several patients with Type 2 DM (T2DM) [2]. In a number of these patients, a sustained glycaemic control cannot be achieved despite using a combination of the conventional oral antidiabetics drugs (OADs) [3,4].

Incretin mimetics may provide a solution for these particular cases and because they provide novel beneficial effects, they may change DM treatment guidelines in the future. Incretins are intestine hormones that act paracrinally and endocrinally in the organism and affect glycaemic control, trophism to the pancreas and body weight [5]; however, due to their short half-life, in vivo effects cannot be obtained with exogenous administration of natural human incretins. To overcome this limitation, incretin mimetics with a more adequate half-life have been developed [6]. This review gives a general scope of the action of natural human incretins, mainly glucagon-like peptide-1 (GLP-1), and describes the actions of two incretin mimetics: liraglutide and exenatide. It also provides a brief description on alternative strategies to protract incretin action.

2. Goals of therapy and current best practice

As DM is a chronic, progressive and yet incurable disease, several parameters constitute therapeutic targets that need to be controlled to attain a good metabolic control over time (Table 1). Some of these parameters are fasting glycaemia, postprandial glycaemia and HbA1c. However, because most Type 2 diabetic patients show not only a poor glycaemic control but also dislipidaemia, hypertension and can be
Exenatide and liraglutide

Table 1. Therapeutic targets in diabetic patients [54,56].

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Therapeutic target</th>
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<tbody>
<tr>
<td>Fasting glycaemia</td>
<td>≤ 126 mg/dl</td>
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<tr>
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<td>≤ 180 mg/dl</td>
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<td>HbA1c</td>
<td>≤ 6.5% (IDF) or ≤ 7% (ADA)</td>
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Table: Therapeutic targets in diabetic patients

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Blood pressure 120 – 80 mmHg

Incretin mimetics are a potential means to achieve these goals [6]. Incretin mimetics act on glucagon secretion, gastric emptying or short-acting insulin analogues will maintain homeostasis in T2DM only a basal-bolus regimen (neutral protamine Hagedorn control in some patients. With the progression of progress, basal insulin starts to be essential to achieve metabolic control in patients with T2DM. The scheme is assessed by periodically determining HbA1c.

In T2DM, insulin resistance is accompanied by declining β-cell function resulting in a large spectrum of conditions that require different prescriptions. Typically, at the moment of T2DM diagnosis, global β-cell function is reduced by 50% [9]. Oral antidiabetics (both insulin sensitisers and secretagogues) are useful during the first stages of the disease when insulin resistance predominates and a pancreatic reserve is still available. But, as pancreatic impairment progresses, basal insulin starts to be essential to achieve metabolic control in some patients. With the progression of T2DM only a basal-bolus regimen (neutral protamine Hagedorn or long-acting insulin analogues combined with short-acting insulin analogues) will maintain homeostasis in many patients [10].

Currently, no treatment can restore a physiological profile of insulin secretion without risk of hypoglycaemia and weight gain. Moreover, there are no available drugs that are capable of acting on glucagon secretion, gastric emptying or β-cell mass. Incretin mimetics are a potential means to achieve these goals in diabetes therapy [6].

3. Endogenous incretins: physiology

It is necessary to understand the mechanism of action of endogenous incretins to achieve a comprehensive approach to the role of incretin mimetics in the treatment of T2DM. Incretin function has been an object of research since the early 1980s, and there is now a solid body of evidence demonstrating its beneficial effects in metabolic control [5]. Figure 1 shows the metabolic effects of GLP-1 and their interactions.

A role for an intestinal factor playing an important role in insulin secretion has been suggested by the observation that oral ingestion of glucose generated a better insulin response than intravenous glucose administration [11,12]. Further investigations showed that GLP-1 not only stimulates insulin secretion but also does it according to the ambient glucose level [5]. This is because GLP-1 can stimulate insulin secretion only when β-cells possess an appropriate range of ATP:ADP ratio. This postprandial profile of insulin secretion is more physiological and targets a crucial aspect of glycaemic control: postprandial hyperglycaemia. Naturally, this autoregulated mode of action provides a more secure metabolic control with a lower risk of hypoglycaemia [5].

Among the incretins that have been investigated with therapeutic purposes, GLP-1 and glucose-dependent insulino-tropic polypeptide (GIP) have given the best results [13]. These are members of the glucagon peptide superfamily and are both secreted in the intestine. GIP is secreted by the K-cells predominant in the duodenum and proximal jejunum, and GLP-1 is secreted by the L-cells in the ileum and colon. Despite its distal location, circulating levels of both GLP-1 and GIP increase within minutes after food ingestion. This suggests that the release of GLP-1 is not only stimulated by endocrine signals, but also by neural signalling [13]. Both peptides are rapidly inactivated by dipeptidyl peptidase IV (DPP IV), a highly specialised aminopeptidase (identical to the lymphocyte surface glycoprotein, CD26) that removes dipeptides only from proteins with the N-terminal penultimate proline or alanine [14]. Through DPP IV action, the biologically active form of incretins is converted into a truncated inactive metabolite [15]. DPP IV is found in the plasma membrane as a homodimer with a molecular mass of 220 – 240 kDa. Its C-terminal domain probably forms an α/β-hydrolase fold. The expression of DPP IV on epithelial, endotherial and lymphoid cells is compatible with its role as a physiological regulator of a number of other peptides of the immune and neuroendocrine systems. However, a family of related enzymes that includes DPP VIII and -IX is now known to be responsible for certain functions previously ascribed to DPP IV [16].

In addition to DPP IV, peptidase NEP 24.11 can inactivate GLP-1. This ectopeptidase is expressed on the surface of a specific line of pancreatic β-cells, the RINm5F line [17].

It was demonstrated that intense treatment of Type 2 diabetic patients with sulfonylureas, metformin or insulin improved their HbA1c levels; however, this effect was not sustained in many patients, and HbA1c levels increased after 4 – 6 years despite an adequate adherence to treatment [8,18]. An explanation for the lack of sustained glycaemic control with conventional diabetes treatments might be that sulfonylureas stimulate insulin secretion with high efficacy but with a high cost: a possible pancreatic exhaustion due to an increased rate of β-cell apoptosis [19]. However, this hypothesis remains highly controversial because pancreatic exhaustion would eventually occur with T2DM progression irrespective of treatment with sulfonylureas. It has been proposed that GLP-1 may not only delay but also reverse the loss of β-cell mass by inhibiting apoptosis and stimulating differentiation of ductal cells into β-cells. This could be mediated, at least in part, by pancreas duodenum homeobox-1 (PDX-1) upregulation.

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LDL ≤ 100 mg/dl (or ≤ 70 ideally)
Blood pressure 120 – 80 mmHg

ADA: HbA1c; Glycosylated haemoglobin; IDF:...
These effects of GLP-1 could ultimately affect the progression of DM and thus incretin action may represent a real innovation in DM treatment and potentially in DM prevention [5].

Another result of GLP-1 action that contributes to its glucose-lowering effect is the reduction in glucagon secretion exclusively during hyperglycaemia [5]. Thus the counter-regulatory response is not impaired during hypoglycaemia and the risk of hypoglycaemia is negligible [20]. This is an interesting property of GLP-1 for Type 2 diabetic patients because they are often characterised by hyperglucagonaemia [21].

Regarding appetite, a reduction in food intake as well as an increase in satiety has been attributed to GLP-1 [22]. Although these effects can be partially explained by the fact that GLP-1 slows gastric emptying, other factors may be involved in this effect [23-25]. It has been suggested that GLP-1 has central nervous actions (specifically in the hypothalamus in which receptors to GLP-1 have been found in rats) that may induce satiety [26]. However, other reports show the absence of GLP-1 receptors in the CNS [5]; thus the complete mechanism of appetite regulation by GLP-1 remains unclear.

The physiology of GLP-1 in diabetic patients is of particular interest. Unlike GIP, the insulinotropic effect of GLP-1 is preserved in patients with T2DM [27]. However, the GLP-1 response during the first 240 min after the start of a meal was significantly decreased in T2DM patients [28]; thus the full incretin effect seems to be reduced in T2DM patients.

4. Incretin mimetics: exenatide and liraglutide

Two strategies have been developed to protract the half-life of endogenous incretins to make them suitable for DM treatment: development of an incretin mimetic resistant to degradation by DPP IV; and inhibition of DPP IV. This review focuses on the first of these strategies. Nevertheless, it must be noted that inhibitors of DPP IV are of increasing interest because they might enhance the physiological effects of incretins when administered orally and once daily [15]. Moreover, it has been reported that a specific DPP IV inhibitor (LAF-237 100 mg/day for 1 month) reduced glycaemia, sustained insulin level and reduced glucagon secretion in Type 2 diabetics [29]. LAF-237 has also been shown to prevent the deterioration of glycaemic control when added to metformin in T2DM treatment for periods of 12 and 52 weeks [30].

4.1 Drug formula and physicochemical properties

Exendin-4 was first isolated from the saliva of the lizard Heloderma suspectum (Gila monster) and is the naturally occurring form of exenatide (AC-2993, synthetic exendin-4) [6]. It is a 39 amino acid peptide agonist of the GLP-1 receptor [3,31] and its amino acid sequence is 53% identical to that of GLP-1 [6]. The main difference is that exenatide contains a glycine instead of an alanine at position two and is thus scarcely recognised by DPP IV [31,32]. Consequently, exenatide is resistant to proteolytic inactivation and has longer plasmatic and biological half-lives [6], which result in both a superior insulinotropic effect and glucose-lowering potency in vivo than GLP-1 [2,31,32]. It is supplied by subcutaneous injection as a clear, sterile and isotonic solution from a glass sealed unit assembled in a pen injector available to deliver unit doses of 5 – 10 µg b.i.d. [33]. The therapeutic schedule currently recommended for exenatide is to initiate treatment at 5 µg b.i.d. within 1 h before morning and evening meals. After 1 month of therapy, the dose can be increased to 10 µg b.i.d., depending on the clinical response [33].

Recently, promising results have been obtained with an extended-release formulation of exenatide in rats as reflected...
in improved levels of HbA$_{1c}$, β-cell secretion and insulin sensitivity. In these studies, a single dose of this formulation provided enhanced glycaemic control for 28 days. The strategy to protract the release of exenatide was to pack a combination of 2% sucrose, 0.3% (NH$_4$)$_2$SO$_4$ and 3% exenatide in poly-lactide-glycolide microspheres.

Liraglutide is an Ala34Arg GLP-1(7-37) analogue substituted on the ε-amino group of the lysine in position 26 with a Glu-spaced palmitic acid developed by Novo Nordisk A/S [34]. The palmitic acid moiety allows liraglutide to bind to the M3 site on albumin, allowing for a protracted action of the compound [2]. Regarding production, recombinant DNA technology and expression in a Saccharomyces cerevisiae strain are used in the manufacturing of liraglutide. Purification is through reversed phase chromatography and the drug can be precipitated and lyophilised [34]. The compound is a colourless liquid, free from turbidity, with a pH near neutral.

### 4.2 Pharmacokinetics

After subcutaneous injection either in the thigh, abdomen or upper arm, exenatide was reported to reach peak plasma concentration in 2.1 – 3 h [33,35,36]. The area under the curve increased proportionally over the dose range of 5 – 10 µg. With reference to its distribution, it does not seem to bind highly to tissues; therefore, a volume of distribution after intravenous infusion of 64 ± 7 ml/kg has been described [33,35,36]. Furthermore, it did not cross the human placental barrier in an in vitro study [37]. Regarding its metabolism and elimination, it is highly resistant to DPP IV degradation and thus its half-life is longer than that of GLP-1 [33]. It has been concluded that the mean terminal half-life of exenatide is 2.4 h [32]. Finally, it is cleared from plasma and eliminated by the kidneys at a rate of 9.1 l/h by glomerular filtration and subsequent proteolytic degradation. Exenatide is measurable in plasma 10 h after dose administration [33].

Liraglutide presents a relatively slow absorption (time to maximum concentration [T$_{max}$]: 9 – 14 h) and a half-life of 12.6 ± 1.1 h. These properties are suitable for once-daily dosing. The accumulation ratio was calculated to be 1.4 – 1.5, which seems to be in agreement with the observed half-life [38,39]. Absolute bioavailability was determined to be 55% based on comparison between subcutaneous administration at a dose of 5 µg/kg and intravenous administration. Liraglutide binds to albumin, thus preventing DPP IV metabolism – apart from the poor recognition by this enzyme – and reaches tissues rapidly after subcutaneous injection. Liraglutide renal filtration is low, with an elimination half-life of 11 – 15 h [38]. As liraglutide consists of amino acids and a fatty acid, it is highly probable that the excretion involves the catabolic pathway for amino acids and fatty acids. None or only slight inhibition of the cytochrome P450 enzyme activities studied was observed in human liver microsomes.

### 5. Metabolic actions of exenatide and liraglutide

It is worth mentioning that although exenatide and liraglutide share most GLP-1 properties, some minor differences exist. Exenatide has already been launched into the market and has concluded mandatory clinical trials for approval, whereas liraglutide is entering Phase III studies.

#### 5.1 Insulin secretion

Liraglutide and exenatide are able to stimulate insulin secretion in conditions of hyperglycaemia or euglycaemia but not during hypoglycaemia, a property termed glucose-dependent insulinotropism. This property is important as it allows these compounds to exhibit a low potential of producing hypoglycaemic events [6]. In Type 2 diabetic patients, not only did exenatide significantly restore first-phase insulin response (major insulin secretion during the first 10 min following intravenous glucose administration, typically absent in these patients) but it also increased second-phase insulin secretion. Moreover, the counter-regulatory response during hypoglycaemia is preserved [38]. In a study that included diabetic and non-diabetic patients, an exenatide infusion was initiated during the use of a hyperglycaemic glucose clamp technique [40]. Plasma insulin response was potentiated by 4 – 5-fold in both diabetic and non-diabetic groups. When glycaemia was intentionally decreased for 1 h, plasma insulin also fell and insulin response increased 10-fold when hyperglycaemia was re-established [41]. Lastly, a dose-dependent increase in fasting insulin concentrations was described during a 3-h exenatide infusion [42].

Similarly, liraglutide only seems to enhance insulin secretory response under glucose infusion when plasma glucose is ≥ 6 mmol/l (~ 108 mg/dl) [43].

As with GLP-1, liraglutide and exenatide have an insulinotropic effect that stimulates insulin release from pancreatic β-cells. Therapy with sulfonylureas and insulin is associated with risk of hypoglycaemia, whereas the insulinoactive action of GLP-1 is attenuated as ambient glucose fall. This glucose-dependent mode of action is mediated by intracellular signalling mechanisms that rely on a high ATP:ADP ratio, which is generated by the glucose–glycolysis signalling pathway.

#### 5.2 Glucagon secretion

It has been reported that glucagon serum concentrations are reduced after exenatide therapy [4,6,31,32] and, as a result, hepatic glucose output would be diminished, contributing to the overall hypoglycaemic effect of the drug [6]. This is an important property of exenatide at the moment of explaining glycaemic reduction in Type 1 diabetic patients because insulin levels usually cannot be increased [43]. Throughout euglycaemia or hyperglycaemia, plasma glucagon was reported to decrease by 50% compared with placebo and to augment during hypoglycaemic periods [42]. In addition, increments in cortisol, adrenaline, norepinephrin
and growth hormone during periods of hypoglycaemia were similar when comparing exenatide with placebo [42]. It is expected that liraglutide will show similar characteristics in Phase III studies. As seen in patients with T2DM in a 1-week trial with liraglutide 6 µg/kg q.d. s.c. injection and 1 week of once-daily placebo injection in a double-blind, cross-over design, the 24-h area under the curve for glucagon was significantly reduced with liraglutide [44]; however, counter-regulation during hypoglycaemia was not affected and when the hypoglycaemic stimulus was triggered, glucagon was secreted normally with liraglutide and with placebo [20].

5.3 Improvement of β-cell mass and function
Improved β-cell mass is a crucial topic in view of the fact that enhancing β-cell mass could prevent or even reverse diabetes progression and provide long-term improvement in the glycaemic control. The reported means in which these would be achieved are: stimulation of β-cells neogenesis/proliferation; and inhibition of their apoptosis [6,31,38]. There are several transcriptional factors that regulate the development of the endocrine pancreas [6] and exenatide has been reported to modulate some of them. First, it stimulates PDX-1-IDX, which is essential for β-cell growth and maturity. Besides, exenatide could stimulate the differentiation of nonfunctional cells, such as ductal, periductal or acinar cells into functional β-cells. Moreover, exenatide would drive multipotential progenitor cells that express GLP-1 receptor to differentiate into β-cells and to stimulate other pancreatic cells in an autocrine or paracrine way. The latter is developed by exenatide with a 10-fold greater potency than GLP-1 [6]. Finally, in one study, it has been demonstrated that exenatide not only upregulates the expression of PDX in human foetal pancreatic cells but also improves their differentiation from precursors and their maturation, thus increasing the functioning β-cell number [45].

Concerning liraglutide, it seems that β-cell proliferation is an early effect that is seen a few weeks after the development of the therapy. Moreover, preclinical data suggests that proliferation and neogenesis occur when glucose and other parameters are not fully controlled compared with the controls. In a study carried out by Bregenholt et al. [46], it was demonstrated that GLP-1 receptor activation had an antiapoptotic effect on both cytokine- and free fatty acid-induced apoptosis in primary islet cells, thus suggesting that liraglutide may be useful for preserving β-cell mass in both Type 1 and 2 diabetic patients. The antiapoptotic effect of liraglutide is cAMP mediated and could be better than that observed with native GLP-1. Both liraglutide and native GLP-1 interact with the GLP-1 receptor. Whether it is the longer half-life of liraglutide, the supraphysiological dosage or other intrinsic property is still unclear in explaining why liraglutide is a better β-cell regenerator than GLP-1.

The way in which this effect is going to be assessed in humans is still not known. There are a number of difficulties and challenges associated with this, including the measurement of the pancreatic islets in vivo and, furthermore, if these cells would be functional with regards to insulin secretion.

5.4 Glycaemic control
Glycaemic control is strictly related to all of the factors described (see Sections 5.1 – 5.3) and is one of the most studied areas of these novel drugs. In healthy volunteers, exenatide reduced glycaemia without leading to hypoglycaemia or any effect on parameters such as blood pressure or pulse rate. Glycaemia decreased in a dose-dependent way [31,42,47,48]. Thus a subcutaneous infusion of exenatide in Type 2 diabetic patients already being treated with diet or metformin revealed a dose-dependent glucose level reduction [31]. Moreover, in Type 2 diabetic individuals treated with sulfonylureas and/or metformin without attaining HbA1c levels of < 8%, exenatide was administered two or three times daily, achieving a significant decrease in postprandial hyperglycaemia and reductions in both fructosamine and HbA1c [31,36,37]. Furthermore, fasting and postprandial glucose were markedly reduced in diabetic patients who only received exenatide [4,32]. Finally, in Type 1 diabetic patients who had insignificant endogenous insulin secretion, subcutaneous exenatide administered 15 min before breakfast with usual insulin normalised postprandial glycaemic excursions, reducing them by 90%. This was associated mainly with a lowered gastric emptying and decreased glucagon secretion. Insulinaemia remained unaltered [49]. In conclusion, exenatide significantly reduces fasting and postprandial plasma glucose levels without leading to hypoglycaemia, with a long-term enhancement in glycaemic control, particularly in Type 2 diabetic patients.

With regards to liraglutide, a study reported by Sten Madsbad et al. [50] delivered an interesting amount of evidence concerning liraglutide and its metabolic control. After a 12-week treatment, HbA1c was decreased in all of the groups except for the lowest liraglutide dosage group. The effect of liraglutide increased with duration of treatment, having the largest decreases in HbA1c towards the end of the trial and still decreasing. Patients belonging to the two highest liraglutide dosage groups achieved HbA1c of ≤ 7% after 12 weeks. Moreover, the fasting serum glucose was reduced by ∼ 2 mmol/l (36 mg/dl); this effect was seen after the first week of treatment and this effect was maintained thereafter.

5.5 Delay in gastric emptying
The phenomenon of lowering gastric emptying was described both in healthy and in Type 2 diabetic individuals, and is a dose-dependent effect generally calculated by the paracetamol absorption method [4,25,31,49]. In accordance with GLP-1 actions, exenatide and liraglutide decelerate gastric emptying. This action has a significant role in postprandial glucose excursions and their control, even in patients with normal β-cell function and fasting glycaemia [6]. Thus it is a considerable factor in glucose homeostasis because it could blunt glucose absorption from the lumen of the gut. Moreover, it
can be involved in the satiety feeling that acts in favour of body weight loss, although a study has also demonstrated increased satiety sensation in fasting subjects [52].

5.6 Body weight and satiety
Exenatide reduced food ingestion in healthy volunteers [6,48]. In one study, the overall day intake was reduced by 21% in patients treated with exenatide without any side effect [52]. In Type 2 diabetic patients, a dose-dependent reduction in mean body weight was documented when comparing exenatide 7.5 and 10 µg s.c. with placebo [3]; thus it has been reported that exenatide would promote early satiety [2]. In a study, exenatide 5 – 10 µg administered to Type 2 diabetic individuals (who were already treated with a sulfonylurea) produced a dose-dependent diminution in body weight throughout a 30-week trial [51].

With regards to liraglutide, observations made in preclinical trials yielded a diminished food intake as studies grew in weeks. Naturally, this reduced food intake was coupled with weight loss as seen in female Goettingen minipigs (an extremely hyperphagic animal) and rhesus monkeys. Although weight loss is ~ 2% in humans, the fact of attaining glycaemic control without weight gain in this patient population [43,50,53,54] is still encouraging. A more enthusiastic result was obtained in a very interestingly designed placebo-controlled, randomised, double-blind, cross-over study in which a reduction of 27% in energy intake in patients with Type 2 diabetes was found when comparing GLP-1 infusion with saline placebo [52]; however, further studies will elucidate this issue of specific interest.

6. Adverse effects of exenatide and liraglutide

Both with exenatide and liraglutide, the most commonly observed side effect was a dose-dependent mild nausea, mostly at the beginning of the treatment [31,51] although in some studies severe nausea in 5 – 6.5% of the patients was reported [3,51]. These were worse when associated with metformin [2,36]. A two-arm, triple-blind, randomised multi-centre study (in which 123 Type 2 diabetic patients were treated with exenatide) demonstrated the effectiveness of gradual dose escalation in reducing the incidence of nausea, with no loss of metabolic activity [55].

Mild transient hypoglycaemia was reported for both drugs. With regards to exenatide, especially when combined with sulfonylureas, hypoglycaemia not requiring any medical assistance was described [3,35,51]. Referring to liraglutide, although its mechanism of action predicted no hypoglycaemic episodes, a reduced number of minor hypoglycaemias were informed [50,53].

Regarding carcinogenicity, the mandatory question for a substance that increases an organ cell mass is: will it generate tumours in other tissues? Preclinical trials arouse a frightening adverse event with both exenatide and liraglutide: χ-cell tumours in rats. The rationale for this adverse event could be explained by the fact that incretin mimetics bind to GLP-1 receptors in χ-cells, which causes calcitonin release; thus provoking increased calcitonin synthesis. The perpetuation of this stimulation on the parathyroid gland leads to hyperplasia and later to a χ-cell adenoma in rats. Nevertheless, it is a well known fact that rats are prone to χ-cell tumours compared with primates, and they also have an increased frequency of χ-cell neoplasias with vitamin D and alendronate. Furthermore, in 52-week-long studies conducted using liraglutide in nonhuman primates, no increase in plasma calcitonin was observed. In addition, studies in mice using exenatide did not show carcinogenesis at systemic exposures of 95-fold higher than the humans at habitual doses [33].

Of the patients, ~ 20% developed anti-exenatide antibodies without any clinical relevance [35,51]. Ongoing trials on liraglutide are also exploring this issue.

7. Expert opinion

Exenatide and liraglutide have the interesting ability of controlling glycaemic excursions, suppressing glucagon secretion during hyperglycaemia and reducing gastric emptying because they are mimetics of naturally occurring peptides in the organism when given at pharmaceutical concentrations. It seems that there are a few questions that remain unanswered regarding these points.

Weight control and an increase in β-cell mass are the most attractive characteristics of these compounds, but these effects still have to demonstrate that they are real and will remain throughout time. Obviously, β-cell mass increase is a real innovation and certainly a promising hope in both deceleration of Type 2 diabetes when already installed and its probable prevention when the metabolic syndrome is diagnosed.

The step between OAD failure and insulin therapy is the suitable place for these compounds. It would be reasonable to think that these compounds might be included in former stages of the pancreatic exhaustion process. An earlier use of these compounds will only occur if they prove to reverse β-cell apoptosis. In this way patients and physicians will accept a non-insulin injectable therapy, otherwise reluctance from both patients and physicians will be an issue to be solved.

Exenatide was approved by the FDA on 29 April 2005 and it is indicated as adjunctive treatment in Type 2 diabetic patients who fail to achieve an adequate glycaemic control with the use of metformin and/or sulfonylureas [33], whereas liraglutide is still undergoing Phase III studies. Therefore, although they are drugs that belong to the same class, future comparisons might provide more solid differences between them.

In view of the available data on these compounds, some a relevant question would be: will these drugs be adopted as standard practice? The authors believe that they will gain a place in medical practice but to define how significant that place will be (at this time) is premature.
It is very interesting to note that (for once) in diabetes therapeutic research the issue has been addressed from a completely different perspective. Although improving insulin is still a good strategy to develop better standards of treatment, incretins are showing that there are further territories to be explored in the field of diabetes.

Many compounds have emerged as the ultimate solution to diverse diseases and they have subsequently failed to comply with all the generated expectations. It is hoped that this will not be the case of incretin mimetics as a specific indication has been assigned (Type 2 diabetes patients with OAD failure) and the drugs are meeting the expected targets (metabolic control with a very good safety profile). It would be wise not to tie incretin mimetics to this therapeutic step and to bear in mind the possibility that they could be better profited at earlier steps of the disease when there are still a considerable amount of β-cells to be rescued.

Nevertheless, there are topics that still have to be elucidated and constitute limitations to their applicability; therefore, further trials will complete the available information on liraglutide regarding safety and efficacy. As with exenatide, post marketing information will be priceless in defining the future of both drugs.

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### Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (★★) to readers.

Exenatide and liraglutide


   • Interesting trial design to assess liraglutide’s performance.


   • Well-designed trial evaluating exenatide as adjunctive treatment for diabetes.


   • Importance of dose escalation in reducing nausea and vomiting.


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