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Incretin-Based Treatment Strategy - GLP-1 Receptor Agonists (GLP-1R) or So-Called Incretin Mimetics

Jindra Perusicova and Klara Owen
Charles University, Prague,
Czech Republic

1. Introduction

The pharmacotherapy of Type 2 Diabetes Mellitus (T2DM) has, in the past 60 years, been developing in unison with the advances in our understanding of diabetes pathophysiology. As our knowledge developed and changed, so did appear new drugs which better and in more targeted fashion rectified the pathological processes leading to the development of diabetes.

If we look into the history of T2DM treatment, the first antidiabetic medicine was insulin – a hormone. Insulin is without a doubt the most important hormone in regulation of glycaemia. The secretion of insulin in response to increasing glucose levels in the bloodstream postprandially is influenced by several mechanisms in three stages:

> Neuronal (cephalic) phase
>
> Gastro-enteral phase (in response to gastrointestinal hormones)
>
> Nutritional phase (beta cell stimulation in response to nutrients – glucose, aminoacids, FFA)

The gastro-enteral phase has been described many years ago as entero-insular axis. This description has been based on observation that the same glucose load administered orally stimulates higher insulin response than when administered intravenously. The difference has been described as an 'incretin effect'.

However, for decades to come, oral antidiabetics have never been able to capitalise on this mechanisms and took the route of influencing glucose homeostasis via peripheral insulin resistance, endogenous hepatic glucose production, or direct stimulation of beta cells.

Currently, it is understood that glucose homeostasis is governed by complex interaction of several hormones: Insulin, amylin, incretins (GLP-1, GIP and possibly others) in balance with the contraregulatory hormones that include glucagon, cortisol, catecholamines and GH with IGF-1. Our understanding of diabetes pathophysiology has developed from dual basis of insulin resistance (IR) and insulin deficiency (ID), via trio of IR in skeletal muscle, ID in beta cell and increased hepatic gluconeogensis, all the way to DeFronzo's (2009) 'Ominous Octet' of muscle, liver, and β-cell dysfunction, and additionally, fat cell pathology (accelerated lipolysis), gastrointestinal tract (incretin deficiency/resistance), α-cell (hyperglucagonemia), kidney (increased glucose reabsorption), and brain (insulin resistance) disorders.

Such advances in the understanding of the pathological basis of diabetes led, after a long time, to development of new drugs to treat hyperglycaemia of diabetes, notably three quite unique antidiabetics, approved by the FDA (Food and Drug Administration) for clinical use:

- Pramlintide in March 2005
- Exenatide in April 2005, and
- Sitagliptin in October 2006

First experiences with these new drugs were quite varied, ranging from almost euphoria in some authors regarding their ability to lower glycaemia, to quite open scepticism and urging to use the new medicines only to those not reaching adequate diabetic compensation with traditional medication, which is much cheaper and with well documented long term efficacy and safety data.

However, over time new strategies for treatment of DM2T have been developed, with some amendments to treatment guidelines to incorporate the new drugs (ADA 2011) and according to expectations, pharmaceutical companies introduced a host of new molecules, notably in the classes of incretin therapy – incretin enhancers (gliptins) and incretin mimetics (analogues of glucagon-like peptide 1) or, more accurately, agonists of GLP-1 receptor.

We therefore have another hormonal treatment option, apart from insulin, based on the GLP-1 hormone. GLP-1 has been selected as a target for therapeutic intervention due to the fact that it has been demonstrated that Type 2 diabetics have got lower level of GLP-1 in their bloodstream and are somewhat resistant to its action, compared to same-weight same-age nondiabetic individuals. Secondly, GLP-1 is the most potent of known incretins, in stimulation of postprandial insulin secretion.

GLP-1 is a peptide with 30-31 aminoacids, produced from proglucagon in L cells of distal ileum and proximal colon. Its target tissue is in pancreas; it stimulates insulin secretion in beta cells and inhibits glucagon secretion in alpha cells. Its bloodstream level rises 5-10times postprandially, with half-life of just 2 minutes and it exerts its action by binding to a specific receptor. It is excreted by kidney via glomerular filtration and tubular catabolism. Specific receptors for GLP-1 are present not only in the membrane of beta and alpha cells of the pancreas, but throughout the body – in the liver, central and peripheral nervous tissues, in the heart, lungs, kidneys and the gastrointestinal tract (Martin, 2011) A fine tuned cooperation of tissues and organs is needed to achieve normoglycaemia (Table 1.)

Due to GLP-1 action on the suppression of glucagon secretion, and its effect on delaying gastric emptying, it exerts multiple effects on glucose homeostasis: it increases the feeling if satiety, reduces hunger and can lead to a moderate weight loss. It plays a substantial role in DM2T, and the disruption in GLP-1 production and action can lead to impaired glucose tolerance.

In the pancreas, GLP-1 not only influences the production and secretion of insulin in the beta cell, but can also stimulate proliferation and neogenesis of beta cells and was shown to delay their apoptosis (Keating, 2005).

As was noted earlier, Type 2 diabetics suffer from decreased GLP-1 production, have decreased GLP-1 levels in the bloodstream and decreased sensitivity to GLP-1 after it binds to its receptor. The decreased sensitivity of beta cells can be overcome by supraphysiological (pharmacological) doses of GLP-1 receptor agonists. This was demonstrated in vivo by GLP-1 infusion to Type 2 diabetics. However, due to the short half life of GLP-1, which is immediately cleaved by dipeptidylpeptidase-IV enzymes, native GLP-1 is unsuitable for subcutaneous administration.

Pancreas	
	Increase in glucose stimulated insulin secretion
	Increase in insulin gene transcription
	Decrease in glucagon secretion
	Increase in somatostatin secretion
	Increased beta cells responsiveness to glucose
	Neogenesis and proliferation of beta cells
Gastrointestinal tract	
	Delayed gastric emptying
	Decrease in gastric acid production
Cardiovascular system	
	Modest decrease in blood pressure
Central nervous system	
	Reduction in appetite
	Increased production of TSH, LH and corticoids
Fat tissue	
	Increase in insulin mediated glucose uptake in fat cells
Muscle and liver	
	Increase in glycogen production

Table 1. Biological actions of GLP-1

Understanding the production, the promising effects and the pathway of degradation of GLP-1, lead to the development of two classes of drugs. Firstly, drugs that would 'mime' the effect of native GLP-1 and activate the processes following its binding to specific receptor, whilst being resistant to enzymatic cleavage, the incretin mimetics, which act very much like GLP-1, and vary from native GLP-1 only in the substitution in some of its aminoacids. This substitution prevents DPP-IV from binding to the molecule and allows for the GLP-1 like effect to last many hours (Burcelin, 2008).

Secondly, GLP-1 levels in Type 2 diabetics can be increased by reversible inhibition of DPP-IV action, which can be achieved by the other class of incretin-based therapies, the incretin enhancers, also known as gliptins.

In 2008, one of the first reviews of incretin therapy was published by Girard. Let us continue the journey and examine the recent history. GLP-1 is one example how modern diabetology ignored important pathways in regulation of glucose metabolism, notably:

• The action of entero-insular axis,
• Designating DM2T as bi-hormonal disease.

Entero-insular axis, in terms of enhanced insulin response in reaction to orally administered glucose in comparison to intravenous administration, has been discussed earlier.

Unger and Orci, in 1975, proposed a theory of Type 2 diabetes as a bi-hormonal disease, with the crucial role of insulin-glucagon interplay, or more exactly beta and alpha cells interaction, rather than just a disruption in insulin secretion and action, as thought previously.

If we administer insulin to a patient with absolute insulin deficiency, as in Type 1 diabetes, we perform a substitution therapy which leads, to a large degree to a normalisation of physiological functions. Type 2 diabetes, however, is marked by only relative insulin

deficiency where insulin administration only rectifies the pathophysiological processes and re-establishes new equilibrium between insulin sensitivity and insulin levels by overcoming, or compensating insulin resistance. We now know, that type 2 diabetics have got disturbances in the incretin effect produced by gut hormones. After meal stimulation T2 diabetics produce moderately less of the active GLP-1, with relatively preserved action. Moreover, chronic hyperglycaemia of diabetes increases the production and activity of DPP-IV enzymes, increasing the cleavage of active GLP-1 (Perušičová 2009, Asmar 2009) These two mechanisms are probably responsible for the decrease in GLP-1 action in T2 diabetics. Such observation is very important for treatment strategy.

GLP-1 analogues are available for clinical use for 6 years in the US, and for 4 years in Europe. During this time we have been flooded with new data on their action, safety and efficacy in humans. One recent review summarised the most important information known so far thus:

- Confirmed observations
  - GLP-1 stimulates insulin secretion in glucose-dependent manner
  - It increases beta cell proliferation and delays its apoptosis.
- New observations
  - The action of GLP-1 is not limited to only pancreatic islet cells, but regulates the function of many other organs
  - GLP-1 has got marked beneficial effect on the brain and cardiovascular system

These new observations open the way to possible therapeutic use of incretins in the treatment of cardiovascular disease (as is already being investigated for instance by a prospective, randomised 5 year study of liraglutide LEADER: *Liraglutide* Effect and Action in Diabetes: Evaluation of cardiovascular outcome) and obesity (Asmar, 2010).

2. Incretin mimetics

Incretin mimetics are the first class of hypoglycaemic drugs that influence glycaemia not only by modifying insulin secretion and action, but also by lowering increased glucagon levels.

All currently available GLP-1 analogues show the same multiple effects as native GLP-1:

- Increase in insulin secretion
- Increase in proinsulin synthesis in beta cells
- Suppression in glucagon secretion from alpha cells
- Slower gastric emptying
- Increased feeling of satiety, decrease in food intake
- Increase in proliferation and delay in apoptosis of pancreatic cells.

Especially the generally supportive and nutritive effect of GLP-1 on pancreatic islet cell mass is subject to intense study and scrutiny. If was believe, that DM2T can only manifest itself in the presence of the dual defect of insulin resistance and insulin deficiency, then this unique action of this class of antidiabetics could play a crucial role in treatment strategy of Type 2 diabetics.

Experimental studies in vitro on isolated beta cells and in vivo on animals have confirmed the stimulating effect of GLP-1 on beta cell proliferation as well as on their neogenesis. The observed increase in beta cell mass in these studies is also due to the delayed apoptosis which is, in diabetics, mainly increased due to glucotoxicity and lipotoxicity.

Apart from increase in insulin levels, GLP-1 is equally responsible for a significant decrease in glucagon levels. In higher doses GLP-1 leads to delayed gastric emptying and an increase in the feeling of satiety, which is extremely beneficial in weight management of obese DM2T patients. Whether these mechanisms of antidiabetic action of incretin hormones are sufficient to delay or prevent the onset of DM2T remains to be elucidated by valid and long term studies. To date we have the longest experience with exenatide, the first GLP-1 analogue on the market, and its short and long term effects are summarised in Table 2.

Acute administration	Chronic administration
Increase in glucose dependent insulin secretion	Decrease in food intake
Return to bi-phasic insulin response	Decrease in body weight
Suppression of increased glucagon production	Increase in insulin sensitivity
Delayed gastric emptying	Increase in proinsulin synthesis

Table 2. Immediate and chronic effects of exenatide in DM 2T

Every treatment option interests us not only from the viewpoint of efficacy in reducing hyperglycemia, but also in terms of added value, most notably in preventing the development of cardiovascular complications of diabetes. Many experimental and clinical studies investigated potential beneficial effects of GLP-1 and its analogues, demonstrating that such effect really exists, both indirectly, due to decrease in glycaemia, lipid levels and BMI, but more importantly directly, through the effects of:

- GLP-1 binding to brain centres regulating blood pressure and heart rate
- Positive influence on action and survival of cardiomyocytes

In view of available data, many authors conclude that it is highly likely that GLP-1 has positive protective effects on beta cells, neurones and cardiac myocytes (Gautier 2008, Holmes 2009). GLP-1 mimetics can also play a significant role in ameliorating endothelial dysfunction and protecting ischemic myocardial cells. Nathanson (2010) published 13-year observation study of 294 subjects with normal glucose tolerance who developed ischemic heart disease. They found direct link between impaired GLP-1 levels and the development of IGT, but not with DM2T. Also, there didn't seem to be any predictive value of GLP-1 levels in terms of subsequent ischemic heart disease.

Systematic meta-analysis of all published data on incretin-based therapies has been conducted in 2007 by Amori (2007). It reviewed 355 available papers from MEDLINE and Cochrane database to include 29 studies which fulfilled the entry criteria. The authors conclude that GLP-1 analogues:

- Lower HbA1c on average by 0.97% (range -1.13 to -0.81%)
- Lower weight on average by 1.4kg compared to placebo and -4.8kg compared to insulin
- Side effects include nausea (RR 2.9, range 2.0-4.2) and vomiting (RR3.2, range 2.5-4.4)

The effects of GLP-1 and it analogues also excited significant attention of researchers and clinicians. The role of GLP-1 in delayed gastric emptying and suppression of hunger suggest that disruptions to GLP-1 production or action could play an important role in the pathogenesis of obesity.

Such theory has been investigated by a study from 2004 (Lugari et al.), measuring the changes in postprandial levels of GLP-1 and DPP-IV activity which is responsible for the

quick cleavage of native GLP-1. The subjects were 22 morbidly obese nondiabetics (BMI 47.5+-1.8 kg/m2) and 9 healthy, age-matched controls. A standard mixed meal of 700kcal has been administered, and the levels of glucose, insulin, GLP-1, and the DPP-IV activity have been measured 4times in the 120minutes postprandially. Furthermore, the same test has been carried out in formerly morbidly obese patients who underwent billiopancreatic diversion (BPD) and have lost at least 5% of their excess weight (BMI 33.8+-1.1 kg/m2). The authors conclude:

- Morbid obesity is at least in part responsible for the accelerated inactivation of GLP-1. Decreased levels of GLP-1 in turn lead to a decrease in the feeling of satiety postprandially, contributing to the abnormal eating patterns of the obese.
- Plasma hyperactivity of DPP-IV does not seem to be influenced by the degree of obesity. The BPD patients showed short increase in GLP-1 levels post-operatively, but this was probably due to the gut manipulation during surgery.

If accelerated cleavage of GLP-1 in obesity is confirmed in further studies, it could present a useful target for treatment of obesity with selective DPP-IV inhibitors.

Long term effects of incretin based therapies (in case of DM longer than 5 years), are not confirmed yet and we have to wait for the results of currently running trials or the acquisition of our own clinical experience.

Most authors welcomed the development of other classes of drugs, GLP-1 mimetics and DPP-IV inhibitors, however, many questions regarding their long-term efficacy, safety, duration of hypoglycaemic effects, and significance of some of their side effects remain to be answered (Penfornis, 2008; Olansky 2010).

On the other hand, many authors advocate the early use of incretin based therapies, not only DPP-IV inhibitors but also GLP-1 agonists, as first line treatment, or as an early add-on in single metformin failure, as they do not pose the risk of hypoglycaemia and have no or beneficial effects on body weight (Henquin, 2008). If a patient follows a majority of lifestyle recommendations, and in the absence of clear insulin deficiency as measured by low C-peptide, it indeed seems to be prudent to prefer rectifying the underlying pathophysiology and improve, via GLP-1 receptor stimulation, the alpha and beta cell crosstalk, and stimulate insulin secretion in glycaemia dependent manner whilst suppressing glucagon production. One question remains, and that is of the durability of such effects.

It has been newly confirmed, that L cells of intestinal epithelium, producing glucagon, GLP-1 and GLP-2 are not the single source of incretins and that the glucagon gene is present not only in the gut, but in neurons and brainstem cells. Glucagon is produced in alpha cells of pancreatic islets from proglucagon, with chain of 160 aminocids. After the cleavage, two probably inactive fragments remain PG1-30 and PG 72-158. In the L-cells of distal ileum, proglucagon is cleaved to give rise to:

- GLP-1 (PG 7-107 amide), potent incretin regulating insulin secretion, glucagon secretion, gastric motility and appetite,
- GLP-2 (PG126-158), significant regulator of growth and mucosal integrity, and
- Glicentin (PG 1-69), whose function is unknown

All three hormones are eliminated mainly by the kidneys, but significant proportion of GLP-2 and some GLP-1 are cleaved and rendered inactive locally and in liver due to DPP-IV action. This would suggest a more paracrine role of GLP-1 rather than classic endocrine one, and there are significant gaps in our understanding of expression of glucagon genes and tissue specific processes that would help us grasp the whole process (Holst 2010).

3. Incretin-based therapy and cardiovascular risk

GLP-1 improves glycaemia and lowers body weight. Both these effects are significant in lowering the increased cardiovascular risk of DM2T. But we are in possession of many more results and studies targeting this issue. There is evidence that native GLP-1 as well as GLP-1 agonists improve the markers of subclinical inflammation as measured by C-reactive protein (Pannaciulli, 2002). GLP-1 could also improve the production of VEGF (vascular endothelial growth factor), which contributes to improvement of EPCs (endothelial progenitor cells) biological function. Circulating EPCs play an important role in preserving endohelium's integrity by aiding neovascularization and reendothelization after injury (Xiao-Yun X, 2011). A clinical studies in diabetic volunteers confirmed that GLP-1 effect on insulin secretion is accompanied by endothelium protective effect, possibly glycaemia related, by decreasing the circulating markers of oxidative stress (Ceriello, 2011).

Other possible beneficial effects on cardiovascular system have been noted in the role of GLP-1 in renal sodium excretion. Double blind, placebo controlled study in 15 healthy nonobese men and 16 obese men monitored the effect of 3-hour GLP-1 infusion on sodium excretion and glomerular filtration after intravenous administration of 9.9g of NaCl. Infusion of GLP-1 lead to statistically significant increase in sodium excretion in the nonobese from 74±8 to 143±18mmol/180 minutes. In the obese sodium excretion increased from 59 to 96 mmol/180 minutes and the hydrogen excretion decreased from 1,1 to 0,3 pmol/180 minutes. At the same time, glomerular filtration decreased from 151 to 142 ml/min in the obese. Authors conclude, that GLP-1 potentially has renoprotective effects, thanks to its action in the proximal tubulus (Gutzwiller, 2004).

4. GLP-1 receptor agonists

4.1 Exenatide

Exenatide was the first GLP-1 receptor agonists introduced into clinical practice. The evaluation of it efficacy and safety in the phase III of clinical trials showed, that as an add-on to sulphonylureas, metformin, thiazolidinediones or their combinations (Buse, 2004; Kendall, 2005) exenatide can achieve the decrease in A1c of 0.8–1.0 percentage points. Moreover, exenatide lead to the significant decrease in weight, by 1.5–3 kg in the first 30 weeks of trials, which continued in the extension of up to 80 weeks, reaching the average 4–5 kg. At the same time, depending on the weight loss achieved, the parameters of cardiovascular factors improved. A decrease in blood pressure, triglyceride levels and an increase in HDL cholesterol levels have been noted, at 30 weeks not statistically significant, but at 3.5 years of follow-up reaching statistical significance. In preclinical trials, exenatide infusion showed beneficial effects not only on beta cells, but also on alpha cells of pancreatic islets, as measured by the insulin/proinsulin ratio and the glucagon levels.

These three pivotal (randomised, placebo controlled and double blind) studies, that have been twice extended, are the *cornerstone of introducing GLP-1 analogues into clinical practice.*

These results also make exenatide one of hypoglycaemic drugs that have the potential to improve atherosclerosis risk factors and thus it has been studied to confirm the possible beneficial influence of incretin-based therapies on cardiovascular system.

It has been confirmed that, similarly to native GLP-1, exenatide can influence other clinical parameters, which in turn can change glucose tolerance of the patient:

- Regulation of satiety and gastric emptying,
- Regulation of water and electrolyte balance

4.1.1 Mechanism of action

Exenatide acts as a replacement of insufficient native GLP-1 level. However, as it is administered in non-physiological route, subcutaneously into peripheral circulation, the circulating levels reach into pharmacological, i.e. significantly higher than physiological amounts of endogenous GLP-1. Such substitution treatment is warranted as the lower GLP-1 levels are found already at the time of DM2T diagnosis, partly due to the hyperglycaemia induced hyperactivity of DPP-IV enzymes. If, after hyperglycaemia is reduced due to improved lifestyle or due to metformin administration, and reduced GLP-1 levels persist, the administration of GLP-1 analogues is a natural next step.

However, in the current clinical practice we cannot measure GLP-1 levels, and therefore we have to wait for the results of clinical studies that would help us identify the patients who would benefit the most from GLP-1 administration.

4.1.2 Tolerability

Exenatide tolerability remains problematic in ca 10-40% patients, where gastrointestinal side effects –nausea, vomiting, and diarrhoea- lead to treatment discontinuation in part of the patients. It has transpired, however, that correct timing of injections in relation to meals, coupled with reassurance about transience of these unwanted effects can significantly modify the numbers of treatment withdrawals by patients.

4.1.3 Safety

All experimental, preclinical and first clinical studies sufficiently demonstrated the safety of exenatide. After few years of clinical use in DM2T, sporadic cases of acute (even hemorrhagic) pancreatitis have been reported, where the connection with exenatide treatment cannot be ruled out. So far, the reports have been confined to individual case-studies, similar to some pancreatitis reports in treatment with DPP-IV inhibitor, sitagliptin (Anderson SL, 2010). *We will refer to the safety issues in detail in the chapter Side-effects.*

4.1.4 Indication and contraindications

Exenatide is a new drug, whose exact place within the range of antidiabetic medication will no doubt change over time. At the moment, exenatide is recommended as a second line treatment in obese DM2T patients with metformin failure, or in patients failing to reach targets on dual OAD therapy.

Contraindications are end stage renal disease and severe gastrointestinal disease in history, including severe hepatic failure and possibly history of acute pancreatitis.

4.1.5 Dosage, combinations, excretion

Exenatide (Byetta) is available in 5 or 10 microgram per dose pre-filled pens. It is recommended to start with 5ug dose twice daily for the first 1 moth of treatment, increasing to 10ug subsequently. Administration sites are identical to insulin's – stomach, thighs or upper arms subcutaneously, 60 minutes before breakfast or dinner.

Exenatide can be combined with all other classes of OAD's. When administering sulphonylureas and exenatide at the same time, higher risk of hypoglycaemia is present. The risk of hypoglycaemia can be minimised by lowering the dose of sulphonylurea. Exenatide is not licensed for concomitant use with insulin.

Exenatide in monotherapy does not lead to hypoglycaemia in diabetics or in healthy subjects.

The maximum levels of exenatide in bloodstream are reached 2 hours after administration. It is primarily excreted by the kidneys.

4.1.6 Side effects

4.1.6.1 Gastrointestinal

As was mentioned repeatedly earlier, gastrointestinal side-effects have been the most common in exenatide – firstly nausea, often very unpleasant and protracted, sometimes coupled with vomiting or diarrhoea. Such unwanted side-effects are present, according to different authors, in 15-50% of patients in the first days to weeks of treatment, and lead to treatment discontinuation in approximately 6-10% of patients. In the remaining patients, these side effects improve and disappear in 3-5 weeks. Nausea was originally suspected to be driving the weight loss, but this assumption has been abandoned due to the two observations:

- Those who lost weight were both from the group with nausea and other GI side effects, and from the group without;
- The decrease in weight is not present only in conjunction with GI side effects, but is longer lasting and progressive (up to 3 years according to current recorded data).

4.1.6.2 Antibodies production

Exenatide is peptide, and therefore capable of inducing antibodies production, according to studies in ca 40-50% of patients, but their effect on safety and efficacy is deemed minimal. It is however possible, that in small minority of patients with high titres of antibodies, exenatide will not be as effective as in others (Russell-Jones, 2010).

4.1.6.3 Acute pancreatitis

From a clinical point of view, acute pancreatitis is a serious adverse event. In 2007, FDA issued a warning about possible link between exenatide use and acute pancreatitis. By 2008, 6 cases of acute hemorrhagic pancreatitis have been reported, 2 of which were fatal. This lead to a host of studies examining the link.

Results have been equivocal. Experimental studies in rats (N=10) who were given exenatide for 75 days, compared to controls (n=10) showed greater degree of acinar inflammation, more pycnotic nuclei, higher lipase concentrations in bloodstream and smaller pancreatic mass in exenatide treated rats compared to controls. (Nachnani, 2010; Ayoub, 2010).

In contrast, studies in mice showed that activation of GLP-1 receptors increases pancreatic mass and selectively modulates expression of genes active in pancreatitis, however, activation or elimination of GLP-1R signal pathway had no effect on the severity of pancreatitis (Koehler, 2009).

To elucidate this, Dore analysed the shared database of commercial medical insurers in the US in 2005-200 for instances of acute pancreatitis in exenatide- or sitagliptin-treated compared to metformin- or glyburide/glibenclamide- treated patients. Evaluation was carried out in 27 996 exenatide treated and 16 276 sitagliptin treated patients. During prospective follow-up of 1 year, 0.13 % patients of exenatide and 0.12% patients on sitagliptin have been hospitalised for acute pancreatitis. This number was no different compared to long known and used OAD treatments, metformin or glyburide/glibenclamide (Dore, 2009).

It is therefore important to remind us, that obesity is a known risk factor for chronic pancreatitis and for acute attacks, regardless of DM2T status (Olansky, 2010).

Anderson (2010) reviewed MEDLINE, internet pages of FDA (Food and Drug Administration) and data from Amylin Pharmaceuticals, the producers of Byetta (exenatide). They found 8 cases of acute pancreatitis during phase II and III of clinical testing, and 36 postmarketing reports, 6 of which have been cases of hemorrhagic pancreatitis. Two cases resulted in death. In case of liraglutide, 3 patients have been reported to develop acute, one chronic pancreatitis. According to the authors, these reports may give rise to clinical suspicion; however, more studies are needed to verify causality.

Gallwitz (2010) also cites recent reviews of this serious complication, and arrives to conclusion that exenatide does not increase the risk compared to other glucose lowering agents (RR 1.0: 95% CI 0.6; 1.7).

Finally, in November 2010, a retrospective analysis was published of 786656 DM2T patients treated with sitagliptin, exenatide or other therapy and control group of non-diabetics. The incidence of acute pancreatitis was 1.9 in non-diabetics, 5,6 in diabetic without incretin based therapy, 5.6 in diabetics on sitagliptin and 5.7 cases per 1000 patient years in diabetics on exenatide. The study demonstrated increased incidence of acute pancreatitis in diabetic versus nondiabetic patients but did not find an association between the use of exenatide or sitagliptin and acute pancreatitis (Garg, 2010**).**

4.1.7 Other demonstrated and disputed effects of exenatide

Preclinical experience with exenatide, as well as with liraglutide, showed improved endothelial function. Both molecules also improve sodium excretion, myocardial function and recovery from ischemic injury in animals. In humans, GLP-1 agonists seem to decrease blood pressure regardless of weight loss.

Further experimental data in mice showed significant decrease in intimal thickening after vascular injury. The question remains, whether such effect is mediated by exendin-4 induced suppression of platelet-derived growth factor-induced smooth muscle cells proliferation, or other direct or indirect effects (Okerson &Yan, 2010; Goto, 2011).

The question of cardiovascular risk influence, in the current absence of prospective randomised studies, can only be answered by retrospective reviews. Best, in 2010 analysed retrospective data from LifeLink database in 2005-2009. Patients without the history of myocardial infarction, ischemic stroke, or coronary revascularization procedure in the past 9 months were assigned to the exenatide-initiated or non-exenatide-initiated cohorts. Exenatide group had more obesity, dyslipoproteinemia, hypertension or ischemic heart disease in their history. After exenatide initiation, this group showed smaller incidence of CV events compared to other diabetes therapy group.

Contrary to expectations, large prospective studies (ACCORD, VADT) did not demonstrate superiority of aggressive treatment of hyperglycaemia in lowering CV risk. The reason for this, repeatedly discussed at EASD in 2009 and 2010, is suspected to be the increased incidence of unknown hypoglycemia, triggering a cardiovascular event. Regardless of what the final conclusion will be, it is important to note that incretin mimetics do not cause hypoglycemia by themselves.

Brixner published a study rounding up all metabolic effects of exenatide as followed up in regular outpatient practice. It evaluated 1709 subjects fulfilling entry criteria. The results (Table 3.) are summarised in Table 3. Authors conclude that the proclaimed effects of exenatide in rigorous clinical studies do translate to regular practice (Brixner, 2009).

Decrease after 6 months of exenatide treatment		
HbA$_{1c}$ (%; DCCT)	-0.8 (0.05)	(p<0.001)
weight (kg)	-3.2 (0.14)	(p<0.001)
systolic BP (mmHg)	-1.9 (0.46)	(p<0.001)
diastolic BP (mmHg)	-0.5 (0.27)	(p<0.078)
LDL-cholesterol (mg/dl)	-7.4 (1.7)	(p<0.001)
triglycerides (mg/dl)	-23.2 (6.7)	(p=0.001)
Increase after 6 months of exenatide treatment		
HDL-cholesterol (mg/dl)	+0.87 (0.33)	(p<0.012)

Table 3. 6-month follow up of exenatide added to metformin and sulphonylurea combination in regular outpatient practice.

Apart from other complex metabolic influence of exenatide, we have repeatedly mentioned the delayed gastric emptying as one of the mechanisms of improved glucose metabolism in treatment with GLP-1 agonists. One Swedish paper on experimental animals as well as in healthy volunteers lists other effects of GLP-1 analogues in gastrointestinal tract, notably in intestines: decrease in intestinal motility and antispasmodic effect (Hellström, 2010).

Therefore, when considering other effects of treatment rather than the pure and simple decrease in glycaemia as reflected in A1c levels, where GLP-1 agonists seem to be on par with other hypoglycaemic agents, exenatide is superior to other classes of drugs due to is significant and lasting effect on body weight decrease (DeFronzo, 2005; Buse, 2004; Kendall, 2005).

Such beneficial effect lead to examination of the place for exenatide in relation to combination with insulin. To ascertain which treatment option is more beneficial in rectifying the parameters of glucose and metabolic homeostasis, Davies, 2009 studied Type 2 diabetics with BMI over 27kg/m², with increased cardiovascular risk and not reaching their targets of glycaemic control on two or three OADs. Average age of the 235 subjects was 56.5 years, BMI 34,1 kg/m² and HbA$_{1c}$ 8.65 % (exenatide subgroup) and 8.48 % (glargine subgroup). More than half, 58.5% of the subjects were using double OAD therapy at the beginning of the 26-week study. There was no difference between exenatide or glargine as an add-on to current therapy in terms for A1c improvement. There was, however, statistically significant difference in weight change: exenatide lead to a weight decrease of 2.73kg and glargine to an increase of 2.98kg. The researchers concluded that exenatide as an add-on therapy in obese diabetics lead to slightly better improvement in A1c, coupled with significant improvement in weight, compared to glargine add-on.

Combination of exenatide and insulin can be somewhat difficult to advocate, and from the patient's point of view hard to sell due to the necessity to juggle two injectable medicines, but, with clear clinical benefits as demonstrated by Yoon (2009) and shown in Table 4. In many countries, such combination is still off-label. However, there is accumulating evidence as to the benefit of such combination. Bunck et al. studied 69 metformin-treated DM2T patients into two groups, exenatide add-on and insulin add-on. Exenatide group showed unequivocal improvement in postprandial glycaemia as well as lipaemia, coupled with improvement in oxidative stress markers, when compared with the glargine-treated group after 52 weeks duration (Bunck, 2010).

Duration (months)	HbA$_{1c}$ (%)	weight (kg)	change in insulin dose/day (units)
0–6	-0.66	-2.4	-18.0
6–12	-0.55	-4.3	-14.8
12–18	-0.54	-6.2	NS
18–27	-0.54	-5.5	NS

NB: all changes vs. baseline statistically significant

Table 4. Metabolic compensation with exenatide added on to insulin

There are already some data available on safety and efficacy of these two medicines used concomitantly. MEDLINE search of all results of such treatment were reviewed by Tzefos and colleagues. Despite their reservations, mainly due to the limited number of studies published, they conclude that such combination is indeed safe in Type 2 diabetics. For selected subgroup of patients (obese with high doses of insulin) is such combination more than promising in terms of reducing the necessary doses of insulin whilst achieving clinically significant weight loss (Tzefos, 2010).

Others confirmed, that exenatide treatment added to insulin leads to significant decrease in body weight and decrease in required insulin doses. In another study, insulin doses dropped significantly (mean at baseline to 51 +/- 37 U/day at 12 months). In 25% of the original subjects of this study, insulin has been discontinued altogether after 3 months. Whilst the data regarding weight and insulin doses were more than impressive, the changes in A1c between the groups were minimal (Nayak, 2010).

Our own national and still ongoing follow-up of basic parameters in 359 Type 2 diabetics treated with exenatide, in co-operation with 24 diabetes specialists, showed the following results:

- Gradual, and progressive weight loss, in at least 12 months duration, as shown in BMI decrease (Fig. 1)
- The best effect on A1c lowering in the first months of treatment, after which the improvement tapers off (Fig.2)

4.2 Liraglutide
4.2.1 Structure
The other currently marketed GLP-1 receptor agonist is liraglutide. It has been modified from native GLP-1 by exchanging arginine for lysine at position 34 of the peptide and by attaching glutamic acid to the chain. Liraglutide is therefore 98% homologous with native GLP-1. This molecule binds to serum albumin, extending its half-life, whilst being resistant to cleavage action of DPP-IV. Liraglutide is administered subcutaneously as a isotonic solution which is slowly absorbed into the bloodstream with half-life of 13 hours, allowing it to be administered once daily.

Due to the fact that liraglutide and exenatide both act through the same receptor pathway, the following chapter will highlight only differences between the two compounds, therefore unless stated, both drugs can be deemed clinically very similar.

4.2.2 Excretion
Liraglutide is excreted by both kidneys and liver. Thus in the situation where impaired renal functions often complicate our treatment plan, it allows for liraglutide to be administered to patients with up to moderate degree of renal failure (Jacobsen, 2009).
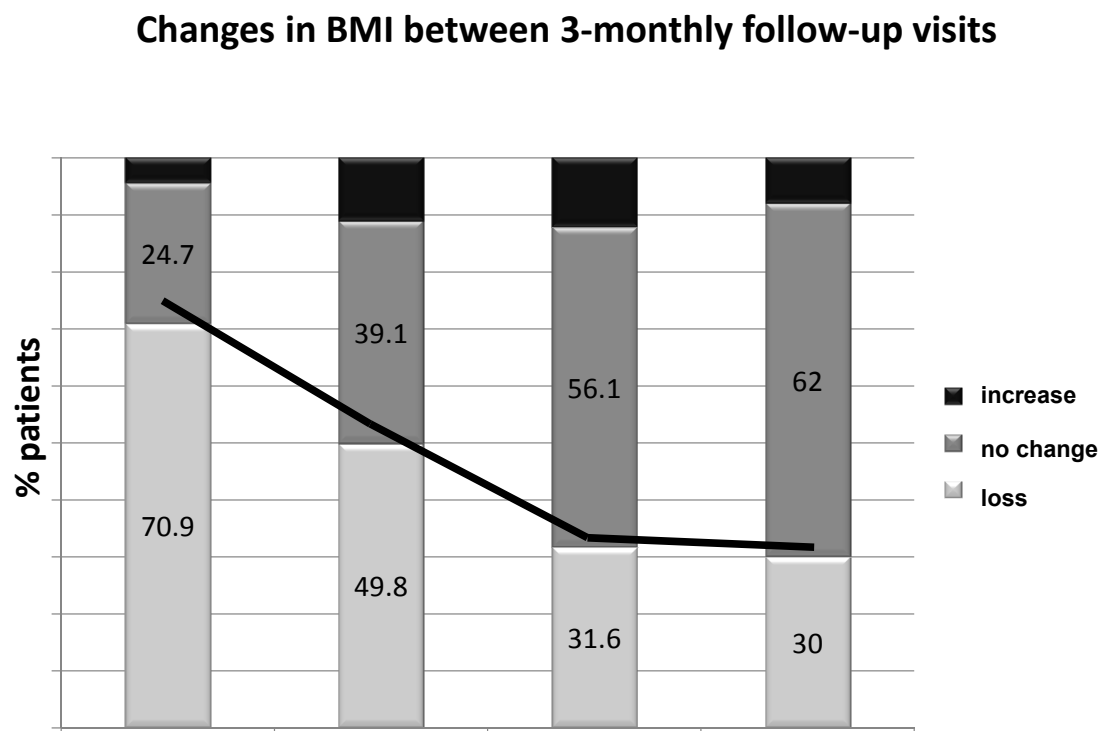
Changes in BMI between 3-monthly follow-up visits

Fig. 1. Changes in BMI after exenatide.

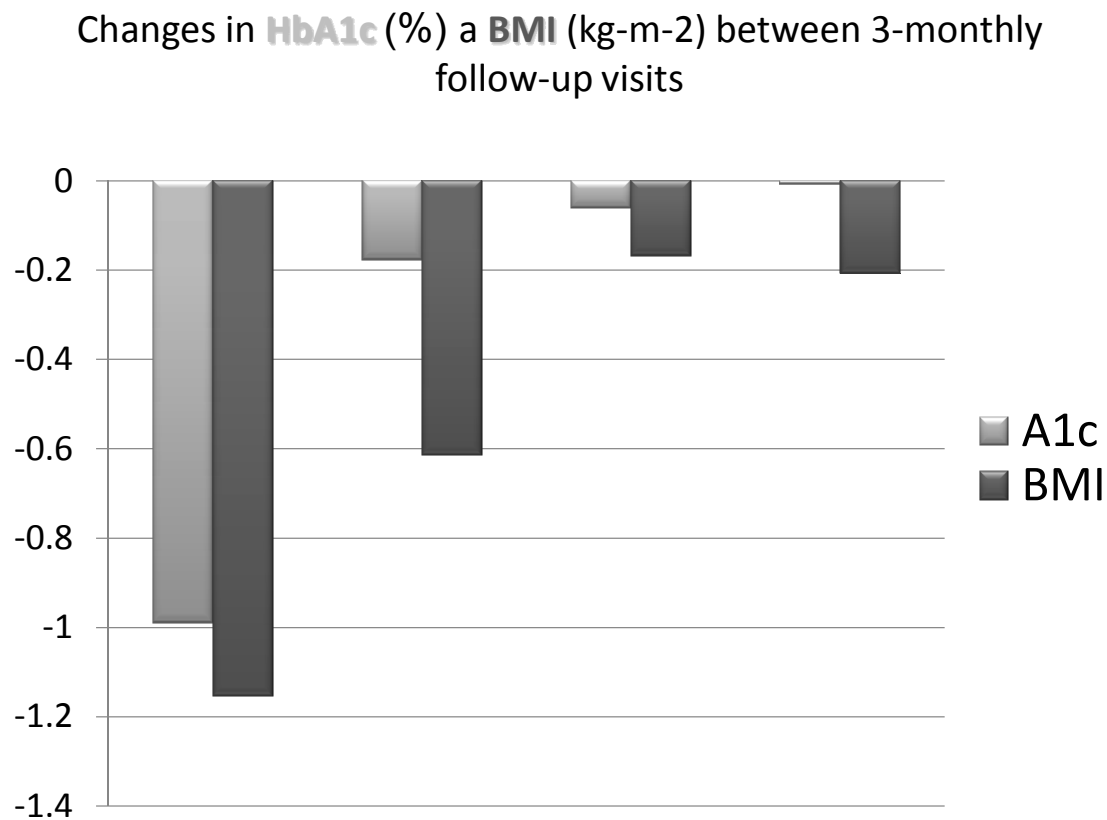## Changes in HbA1c (%) a BMI (kg-m-2) between 3-monthly follow-up visits

Fig. 2. Changes in A1c and BMI after exenatide.

4.2.3 Safety

First, data from studies in rats and mice suggested that liraglutide was associated with an increased risk of thyroid C-cell focal hyperplasia and C-cell tumours at doses that resulted in plasma drug levels similar to those seen in humans at the approved doses (Bjere Knudsen, 2010). However, the incidence of liraglutide-induced medullary thyroid cancer did not affect the overall survival rate among either rats or mice. The relevance of these findings to humans is unknown. The incidence of medullary thyroid cancer is too low to allow for direct comparison with liraglutide exposed group of patients. The only way how to assess potential risk is by monitoring calcitonin. Serum calcitonin levels below 10 pg/ml are consistent with the absence of medullary thyroid cancer, whereas levels above 100 pg per millilitre are highly predictive of medullary thyroid cancer. In trials, calcitonin levels increased slightly more often with liraglutide than in control patients; but were still within normal ranges. Furthermore, data from a long-term study did not reveal any notable difference in mean calcitonin levels between liraglutide and control groups over 2 years of follow-up (Hegedüs, 2011). As it is very difficult to translate animal data to humans, although FDA was satisfied that liraglutide poses no known safety concern at the moment, as a precautionary measure it ordered 15-year long monitoring of medullary carcinoma in liraglutide-treated patients.

Second, liraglutide, similarly to exenatide, has been suspected in inducing acute pancreatitis in patients receiving it, due to postmarketing reports to FDA regarding exenatide and sitagliptin, because liraglutide acts through the same GLP-1 pathway. The FDA-ordered evaluation of such possible risk from data in Phase II and III studies with liraglutide revealed seven cases of pancreatitis reported among the 4257 patients treated with liraglutide and one case in the 2381 patients in the comparator group. After adjustment for more patient-years of exposure to liraglutide, this finding of pancreatitis represented a 4:1 imbalance between the liraglutide and comparator groups. This lead to suggested change in labelling for all incretin-based therapies, about persistent or severe nausea and vomiting which may be early manifestations of pancreatitis and therefore warrant prompt discontinuation of treatment (Parks, 2010).

4.2.4 Efficacy

4.2.4.1 Glycemic control

The series of Phase III trials establishing the role of liraglutide in monotherapy as well as in combination with other antidiabetic medications was called LEAD (Liraglutide Effect and Action in Diabetes). Overall, the studies demonstrated dose dependent effect of liraglutide on glycemic control and body weight. Earlier published studies showed the A1c decrease of 0.33-0.75% and weight reduction of 1.2-1.9kg in doses up to 0.75mg daily, later studies with dosage escalation up to 1.9mg per day showed A1c decrease of up to 1.7% and weight loss of up to 3 kg in longer duration of studies (14 weeks vs. 8-12 in earlier studies). In normal doses (in many countries the maximum approved dose is 1.2mg per day, not the highest 1.8mg/day), liraglutide is not more effective than glimepiride in glycemic control, but its effect if more durable than either glimepiride or glibenclamide. Liraglutide also improves pancreatic cell function with minimal risk of hypoglycaemia (Croom, 2009).

LEAD programme demonstrated that liraglutide administration (Garber, 2008):

- leads to weight loss; the weight loss is greater with greater baseline BMI
- protects beta cells as assessed by HOMA-B model

- improves glycemic control via both improvements in fasting and postprandial glycaemia and HbA1c
- carries virtually no risk of hypoglycaemia
- lowers triglyceride levels
- lowers systolic blood pressure

The overview of all LEAD Studies is provided in Table 5. Other studies also confirm significant improvements in HbA1c levels, significant improvement in BMI and improved beta cell function in monotherapy as well as in combination with metformin, glimepiride or rosiglitazone. It also lowered systolic blood pressure (Drab, 2009).

	N	Duration (months)	Extension (months)	Entry medication	Comparator	δHbA_{1c} (%) [a] liragl.	δHbA_{1c} (%) comp.	δm (kg)[a] liragl.	δm (kg)[a] comp.
LEAD1	1041	6	0	Glimepiride	Rosiglitazon or placebo	−1.1	−0.4	−0.2	+2.1
LEAD2	1091	6	48	Metformin	Glimepirid or placebo	−1.0	−0.7	−2.8	+1.0
LEAD3	746	12	60	none	Glimepirid	−1.1	−0.5	−2.5	+1.1
LEAD4	533	6	0	Metformin + rosiglitazone	Placebo	−1.5	−0.5	−2.0	+0.6
LEAD5	533	6	0	Metformin + glimepiride	Glargine or placebo	−1.3	−1.1	−1.8	+1.6
LEAD6	464	6	3	Metformin and/or glimepirid	Exenatide	−1.1	−0.8	−3.2	−2.9

Table 5. Overview of LEAD trials. Based on Hansen, 2010.
HbA1c at entry was 8.2-8.5%. [a]on 1.8 mg liraglutide

The metaanalysis of published GLP-1 receptor agonists randomised controlled (with active comparator or placebo) studies (total of 21, out of which 6 have only been partially published) of exenatide and liraglutide, evaluated data on 5429 and 3053 patients respectively. The analysis showed significant improvement in glycemic control as measured by improvement in HbA_{1c} (-1.1; -0.8 %) with very low risk of hypoglycaemia. Authors conclude that liraglutide once daily is as efficacious and safe, with comparable tolerability, as exenatide twice daily (Monami, 2009).

4.2.4.2 Effects on body weight

Significant dose-dependent weight loss was demonstrated in all of the LEAD studies. In the monotherapy study (LEAD 3), absolute weight loss was 2.5 kg at the 1.8 mg dose and 2.1 kg at the 1.2 mg dose. Weight loss was greatest in combination with metformin: 2.8 kg with the 1.8 mg dose and 2.6 kg with the 1.2 mg dose (Nauck, 2009). In LEAD 5, the difference

between insulin glargine and liraglutide as an add-on to metformin was 3.4kg, as treatment with insulin glargine increased weight by 1.6 kg, whereas liraglutide decreased weight by 1.8 kg (Russell-Jones, 2009). In LEAD 6, a head-to-head comparison with exenatide, liraglutide at the 1.8 mg dose was superior to exenatide in inducing weight loss of 3.2 kg compared with 2.9 kg in the exenatide group (Buse, 2009). The reduction of body weight with liraglutide is confirmed to result from a reduction in body fat (Jendle, 2009). Overall, liraglutide induces the maximum weight loss in metformin-treated patients, but also appears to offset the weight gain of sulfonylurea, thiazolidinediones, or insulin treatment.

A potential role of liraglutide as a weight loss treatment is emerging. In a recently reported trial of 20 weeks duration, 564 obese individuals with BMI 30–40 kg/m^2 were randomly assigned to one of 4 doses of liraglutide (1.2, 1.8, 2.4, or 3.0 mg), placebo, or orlistat. All subjects were instructed to decrease their calorie intake by 500 a day and to increase their physical activity. Subjects on liraglutide lost significantly more weight than did those on placebo and orlistat. Mean weight loss with these 4 doses of liraglutide was 4.8, 5.5, 6.3, and 7.2 kg vs. 2.8 kg in the placebo group and 4.1 kg in the orlistat group. About 76% of individuals lost more than 5% weight with liraglutide 3.0 mg compared with 30% in the placebo or 44% in the orlistat groups (Astrup, 2009).

4.2.4.3 Effects on cardiovascular risk modification

First concern with any newly developed drug should be its safety. Regarding liraglutide, FDA approved the drug before new guidelines have been published regarding the assessment of safety whereby comparing the incidence of cardiovascular events in the group receiving the agent under investigation with that in comparator groups have to demonstrate that the upper bound of the two-sided 95% confidence interval for the estimated risk ratio was less than 1.8. Analyses of cardiovascular events from the combined phase II and phase III trials showed that liraglutide met the standard for ruling out an unacceptable increase in cardiovascular risk. The overall rates of cardiovascular events in the preapproval clinical trials were low, however, and the FDA is therefore requiring a postapproval study of cardiovascular safety (Parks, 2010).

A welcome and consistent effect of liraglutide in the LEAD programme was the modest reduction of blood pressure, ranging from 2.1 to 6.7 mm Hg (Nauck, 2009, Buse, 2009, Zinman, 2009, Russell-Jones, 2009). GLP-1 has been reported to have a natriuretic effect, which might explain its effect on blood pressure (Gutzwiller, 2004). Compared to exenatide, the effect on blood pressure was slightly more pronounced, but coupled with slight increase in heart rate. (Hattori, 2010; Jackson, 2010; Okerson, 2010).

In terms of actual cardiovascular risk reduction in DM2T, the initial results with liraglutide are promising. Liraglutide lowers the low-grade inflammation of vascular endothelium via:

- Increased production of nitrous oxide,
- Suppression of NF-kB activation, and
- Partially through AMP kinase activation

These effects seem to explain the vasoprotective action of liraglutide, which can, in the longer run, translate to cardiovascular risk factor modification. This, coupled with results of metaanalysis of LEAD studies showing decrease in PAI-1 and CRP levels, and primary improvement in endothelial function by improved vascular wall relaxation, make liraglutide a molecule interesting not only to diabetologists but to cardiologists, too.

Recent experimental work of Noyan-Ashraf, 2009, in mice, showed that liraglutide administration activates cytoprotective mechanisms in myocardium of non-diabetic as well as diabetic animals, and improves survival after acute myocardial infarction.

Poor control of diabetes leads to accelerated development of atherosclerosis, leading to cardiovascular complications. Sullivan and colleagues applied the diabetic model CORE to valid epidemiologic data on morbidity and mortality in clinical studies and simulated the effects on cardiovascular events based on LEAD 1 data, comparing addition of rosiglitazone or liraglutide to glimepiride. The findings in hypothetical 5000 patients slightly favoured liraglutide in terms of survival, when compared to rosiglitazone. However, these are hypothetical results and we have to expect long term safety and efficacy information from postmarketing data (Sullivan, 2009).

4.2.3 Conclusion

Although liraglutide and exenatide act through the same GLP-1 receptor, their different structure leads to some differences in action. This favours liraglutide in allowing once daily administration, irrespective of meal time, at any time of a day. Also, the head to head comparison of liraglutide with exenatide in LEAD 6 suggests that liraglutide is somewhat more effective than exenatide in lowering the blood glucose and HbA_{1c} levels. Liraglutide seems to be more consistent in lowering blood pressure (Pinckney, 2010). Moreover, in terms of tolerability, despite both drugs being well tolerated (again with some shift towards shorter duration of side effects in liraglutide), liraglutide should be less likely to cause hypoglycaemia, and there is no allergy or antibody development, due to higher structural homology to native GLP-1.

All these factors could become unimportant, when new molecules or new formulations become available. The pipeline is in brief discussed in the following chapter.

5. New compounds and formulations in the pipeline

Incretin-based therapies are undoubtedly the fastest developing area of Type 2 diabetes treatment. After the halting of taspoglutide during Phase III studies mainly due to adverse allergic reactions, two molecules are still significantly advanced in the pipeline to be of potential clinical interest. First, extended release exenatide, to be marketed under the name Bydureon, and albiglutide, modified GLP-1 receptor agonist bound with human recombinant albumin, to be marketed under the brand name Syncria.

5.1 Exenatide LAR

In this extended release formulation, exenatide is encapsulated in microspheres made of poly (D,L lactic-co-glycolic acid), a biodegradable polymer, that breaks down over time and allows a controlled rate of drug delivery. In terms of safety, drug interactions and possible combinations with other hypoglycemic therapies, there seems to be little difference between exenatide twice daily and once weekly. We therefore present only studies concerning the differences in efficacy between these two formulations of the same compound.

5.1.1 Efficacy

Our knowledge on the clinical efficacy and safety of exenatide LAR comes, similarly to the LEAD battery of studies for liraglutide, from the group of DURATION 1-5 (Diabetes

Therapy Utilization: Researching Changes in A1C, Weight and Other Factors Through Intervention with Exenatide Once Weekly) studies. We review the results, with the exception of DURATION 4, which, according to the clinical trials website (www.clinicaltrials.gov), has not reported any results yet.

DURATION 1 (Drucker, 2008) was designed as a non-inferiority study of exenatide LAR compared to exenatide BID in patients drug naive, on single or multiple OADs. Long acting exenatide (2 mg once weekly) was found to cause a greater reduction in HbA1c than exenatide 10 μg twice daily (-1.9% vs. -1.5%, mean difference 0.40 (95% CI: 0.12, 0.68), p = 0.005). However, exenatide BID was superior to the once weekly 2 mg regimen in controlling PPG. Exenatide LAR led to greater reduction in TC (-0.31 vs. -0.10) and LDL (-0.13 vs. +0.03) than twice daily exenatide. The study found no difference in weight loss or the percentage of participants losing weight (76% with exenatide once weekly versus 79% with exenatide twice daily). A significantly greater proportion of LAR patients achieved target HbA1c levels of 7.0% or less (77%vs 61% of evaluable patients, p=0.0039). Weight decreased in participants who reported no episodes of nausea throughout the study (70%). Nausea and vomiting were less frequent with once weekly exenatide compared with twice daily exenatide.

This study has been extended to 52 weeks with sustained effects on diabetes control and weight loss maintenance. Patients on exenatide LAR maintained A1C improvements through 52 weeks (-2.0% [95% CI -2.1 to -1.8%]). Patients switching from exenatide BID to exenatide QW achieved further A1C improvements, ‚catching up' those on LAR formulation and achieving same mean A1C (6.6%) at week 52. At week 52, 71 and 54% of all patients achieved A1C <7.0% and <or=6.5%, respectively. In both treatment arms, fasting plasma glucose was reduced by >40 mg/dl, and body weight was reduced by >4 kg after 52 weeks (Buse, 2010).

DURATION 2 studied exenatide LAR as an add-on therapy for patients failing on metformin. This study was designed as randomised, double-blind, double-dummy, superiority trial, comparing exenatide once weekly in combination with oral placebo against sitagliptin 100mg/day and injectable placebo or pioglitazone 45mg/day and injectable placebo. Treatment with exenatide reduced HbA1c (-1.5%, 95% CI -1.7 to -1.4) significantly more than did sitagliptin (-0.9%, -1.1 to -0.7) or pioglitazone (-1.2%, -1.4 to -1.0). Weight loss in the treatment arm containing exenatide (-2.3 kg, 95% CI-2.9 to -1.7) was statistically significantly greater than in the treatment arm containing sitagliptin (difference -1.5 kg, 95% CI -2.4 to -0.7, p=0.0002) or indeed pioglitazone (difference -5.1 kg, -5.9 to -4.3, p<0.0001) (Bergenstal, 2010).

DURATION 3 compared exenatide LAR with insulin glargine (titrated to glycemia of 4.0-5.5mmol/l) in adults with type 2 diabetes with suboptimal control on maximum tolerated doses of OADs (single metformin 70%, metformin + sulphonylurea 30%) for at least 3 months. Exenatide 2 mg once weekly led to slightly greater reduction in TC and LDL than glargine (-0.12 vs. -0.04 mmol/l TC; -0.05 vs. +0.04 mmol/l LDL). There was no difference in triglyceride levels. Change in HbA(1c) at 26 weeks was greater in patients taking exenatide (n=228; -1.5%, SE 0.05) than in those taking insulin glargine (n=220; -1.3%, 0.06; treatment difference -0.16%, 0.07, 95% CI -0.29 to -0.03). Slightly higher number of exenatide LAR patients dropped out of the study (5% vs 1%, p=0.012) due to adverse events (Diamant, 2010).

DURATION 4 was designed to test the hypothesis that exenatide once weekly is superior to metformin, sitagliptin, and pioglitazone in HbA1c reduction at 26 weeks compared to

baseline, in drug-naive patients with type 2 diabetes who are inadequately treated with diet and exercise. To our knowledge, the results of this trial have not yet been reported in the scientific press.

DURATION 5 (Blevins, 2011) was designed as head to head comparison of exenatide LAR and exenatide BID in drug naive (19% of the study population), on single OAD (47%) and on multiple OADs (35%). The results again showed greater efficacy of LAR formulation in lowering HbA1c (-1.6 ± 0.1% vs. -0.9 ± 0.1%; P < 0.0001) and fasting plasma glucose (-35 ± 5 mg/dl vs. -12 ± 5 mg/dl; P = 0.0008). The difference in mean body weight reductions was likewise not statistically significant (-2.3 ± 0.4 kg and -1.4 ± 0.4 kg). The mild and transient nausea, well known in the currently available exenatide formulation, was less common in LAR (14%) than with BID formulation (35%). Injection-site reactions were genrally fairly infrequent, but more common in exenatide LAR.

5.2 Albiglutide

There is paucity of published data on albiglutide, as this molecule is not available anywhere in the world and has not yet been filed for approval, so the majority of the following data is cited from an article by Rosenstock and Stewart, 2010.

5.2.1 Structure

Albiglutide is a GLP-1 receptor agonist macromolecule comprised of two copies of a 30-amino-acid sequence of human GLP-1(7-36) (as a tandem repeat) coupled to recombinant human albumin (rHA). A single substitution (Ala→Gly) at the DPP IV cleavage site confers resistance to degradation, while retaining 97% homology with native GLP-1. The half-life of albiglutide is 5 days, and can be administered at weekly or less frequent intervals.

5.2.2 Side effects

Nausea and vomiting correlated with albiglutide exposure. Compared with biweekly and monthly dosing, weekly dosing of albiglutide had the lowest peak:trough ratio, and also the lowest incidence of GI events (Rosenstock 2009).

There was no increase in documented hypoglycemia with albiglutide (0-3.1%) compared with placebo (3.9%) or exenatide (2.9%). Antialbiglutide antibodies were detected in only 2.5% patients; however, the appearance of antibodies was mainly transient, the antibodies were non-neutralizing, and of low titer. There was no evidence of an association between albiglutide antibodies and efficacy or safety.

5.2.3 Efficacy

There was consistent weight loss in the albiglutide groups (–1.1 to –1.7 kg for patients receiving the highest dose in each schedule) compared with the placebo group (–0.7 kg). The weight loss with albiglutide was numerically less than that observed with exenatide (–2.4 kg) but there were weight differences at baseline between the groups. Albiglutide provided dose-dependent HbA1c reductions within each dosing schedule of the 16-week phase IIb study. In patients receiving the highest dose in each treatment schedule, HbA1c reductions were –0.87%, –0.79% and –0.87%, respectively, from baseline HbA1c of 8.0%, 7.9% and 8.1%, respectively, for 30 mg weekly, 50 mg biweekly and 100 mg monthly, compared with exenatide –0.54% and placebo –0.17% from baselines of 7.8% and 8.0%, respectively. Decreases in both systolic and diastolic blood pressure were also observed, with the group

receiving albiglutide 30 mg weekly experiencing a decrease of –5.8 mmHg and –1.9 mmHg, respectively, for systolic and diastolic blood pressure.

5.2.4 Future
The Phase III HARMONY program will provide the first long-term blinded comparative data on a GLP-1 receptor agonists in clinically meaningful range of combinations whilst also extensively examining positioning of albiglutide in respect to active comparators.

6. GLP-1 summary

Type 2 diabetes mellitus is a well-established risk factor for cardiovascular disease. Therefore all therapeutic modalities used in diabetes have to be evaluated with regard to cardiovascular effects. Incretin-based therapies, and notably GLP-1 receptor agonists are therefore a promising class of antidiabetic drugs.

Sufficient data supports beneficial effects of GLP-1 receptor agonists on: *glycemia, weight, blood pressure* and the circulating levels of *CRP, triglycerides and free fatty acids.*

GLP-1 analogues seem to have beneficial effects on beta cell function (Wang, 2011), protecting beta cells from the harmful effects of *lipotoxicity*. There is, however, a question of timing for GLP-1 analogues in the *natural course of DM2T*, most likely in combination with metformin (Cho, 2011). They can play crucial role in preserving beta cell function. Later in the course, when insulin deficiency prevails, substitution therapy with insulin is warranted.

GLP-1 analogues (GLP-1 receptor agonists) possess unique characteristics and are at the moment the only therapeutic class that influences multiple pathologies inherent to DM2T:

* hyperglycemia;
* beta cell dysfunction;
* alimentary obesity;
* insulin resistance;
* hypertension and dyslipidemia.

6.1 Overall comparison of two first GLP-1 analogues
In general, there seem to be very little clinical difference between the two currently available molecules of GLP-1 receptor agonists, exenatide and liraglutide. Overall, Shyangdan, 2010, provides us with most up to date review and meta-analysis of these two drugs, in comparison between each other and with other classes of oral antidiabetics:

Diabetes control (glycated haemoglobin)
Liraglutide daily was superior to glargine, rosiglitazone, sitagliptin and exenatide BD.
Exenatide twice daily was equivalent to both insulin and rosiglitazone twice daily, taking differences in HbA1c of less than 0.5% as being not clinically significant.
Weight loss
Exenatide and liraglutide caused greater weight loss than all active comparators (oral agents and insulin) - most of which led to weight gain. Weight loss was independent of nausea.
Hypoglycaemia and adverse events
The incidence of hypoglycaemia in combination with metformin is very low. Hypoglycaemia was seen most often when GLP-1 analogues were used in combination with sulphonylureas.

The most commonly reported adverse events with both GLP-1 agonists were gastrointestinal (nausea, vomiting and diarrhoea).

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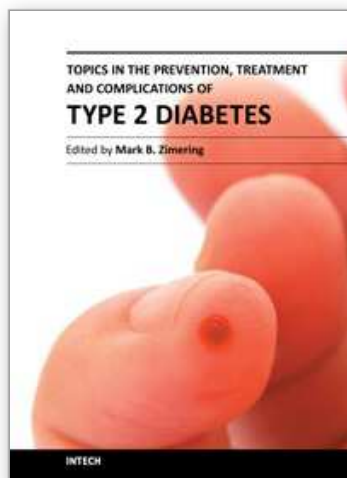
Topics in the Prevention, Treatment and Complications of Type 2 Diabetes

Edited by Prof. Mark Zimering

Type 2 diabetes is estimated to affect 120 million people worldwide- and according to projections from the World Health Organization this number is expected to double over the next two decades. Novel, cost-effective strategies are needed to reverse the global epidemic of obesity which is driving the increased occurrence of type 2 diabetes and to less the burden of diabetic vascular complications. In the current volume, Topics in the Prevention, Treatment and Complications of Type 2 Diabetes, experts in biology and medicine from four different continents contribute important information and cutting-edge scientific knowledge on a variety of topics relevant to the management and prevention of diabetes and related illnesses.

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