# Positioning Glucagon-like-peptide-1-based Treatments within an Optimal Management Regimen for Type 2 Diabetes

*a report by*

**Katrine Bagge Hansen**,[1] **Filip Krag Knop**[2] *and* **Tina Vilsbøll**[2]

*1. Departments of Clinical Physiology and Internal Medicine, Glostrup Hospital, University of Copenhagen;*

*2. Department of Internal Medicine, Gentofte Hospital, University of Copenhagen* DOI:10.17925/EE.2008.04.00.44

Type 2 diabetes is characterised by high blood sugar caused by the inability of the pancreas to produce sufficient insulin, in combination with a loss of the normal reciprocal relationship between glucose and glucagon concentrations in the blood and impaired tissue sensitivity to insulin. In the longer term, high blood glucose concentrations can result in long-term diabetic complications, dramatically increasing the risk of early death. Although a range of different antidiabetic oral treatment options exist, current management of type 2 diabetes is often associated with weight gain and a risk of hypoglycaemia, and a combination of antidiabetic agents is often required. Furthermore, most treatment options do not target the multifaceted patho-physiology of type 2 diabetes. In contrast, newly developed incretin-based therapies of type 2 diabetes employ beta-cell-preserving properties, and may restore reduced glucose-induced insulin secretion in type 2 diabetes. In addition, these agents do not appear to promote weight gain or hypoglycaemia. This review focuses on the position of the incretin-based treatments within an optimal management regimen for patients with type 2 diabetes.

## Incretin Hormones

The term 'incretin effect' refers to the amplification of insulin secretion elicited by hormones secreted from the gastrointestinal tract. The effect is based on the observation that for equivalent levels of glycaemia, oral glucose results in considerably more insulin being released than intravenous (IV) glucose does. It has become clear that augmentation of glucose-stimulated insulin release by hormones secreted from the gut accounts for up to 70% of the insulin secretion following oral glucose ingestion.[1] Two known hormones act as incretins: glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). GIP is released from endocrine K cells distributed primarily in the mucosa of the duodenum and upper jejunum. The release of GIP is tightly linked to the presence, digestion and absorption of glucose and fat in the small intestine.[2,3] GLP-1 is released from endocrine L cells distributed primarily in the mucosa of the more distal part of the small intestine and colon. Secretion is mediated by the presence and absorption of nutrients,[3] but also seems to be mediated by neural signals[4,5] eliciting responses before nutrients have actually reached the small intestine. However, recent observations indicate that GIP and GLP-1 are co-localised in a subset of endocrine cells throughout the gastrointestinal tract.[6–8] This finding may explain the fast secretory responses following ingestion of nutrients, but other mechanisms – for instance, paracrine interaction between the two incretin hormones, as indicated by data in dogs,[9] and intrinsic neuroendocrine mechanisms[10] – may be involved.

After the secretion of GIP and GLP-1, both hormones are degraded by the enzyme dipeptidyl peptidase 4 (DPP-4).[11–14] While GLP-1 is rapidly degraded in the circulation with an apparent half-life of 1–1.5 minutes,[15,16] GIP is degraded more slowly, with a half-life for the intact hormone of seven minutes.[17,18] Both hormones possess strong glucose-dependent insulinotropic properties. They are active with respect to enhancing glucose-induced insulin secretion from the beginning of a meal and they contribute almost equally to the potentiation of post-prandial glucose-induced insulin secretion, but with the effect of GLP-1 predominating at higher glucose levels.[19,20] GLP-1 has an inhibitory effect on glucagon secretion, but this is observed only at glucose levels at or above fasting levels, which implies that GLP-1 does not weaken the counter-regulatory response to hypoglycaemia.[21] In contrast, GIP has been shown to stimulate glucagon secretion. Furthermore, GLP-1 enhances all steps of insulin biosynthesis and insulin gene transcription, improves beta-cell function (and beta-cell mass, according to data from animal experiments) and prevents apoptosis (programmed cell death) of beta-cells.[22] Finally, and very importantly, GLP-1 enhances satiety and reduces food intake, probably due to a combination of activation of GLP-1 receptors in the central nervous system and inhibition of gastrointestinal motility.[23,24]

## Incretin Hormones in Type 2 Diabetes

In 1986, it was shown that the incretin effect is strongly reduced in patients with type 2 diabetes (~30% versus ~70% in healthy

Katrine Bagge Hansen is a Research Fellow on a PhD project in the Department of Clinical Physiology at Glostrup Hospital, University of Copenhagen. Her research concerns incretin hormones and type 2 diabetes. She has clinical experience from post-graduate work at several departments of internal medicine.

E: kabaha01@glo.regionh.dk

Filip Krag Knop is a Physician in the Department of Internal Medicine at Gentofte Hospital, University of Copenhagen. His research is focused on the pathogenesis of type 2 diabetes and utilisation of incretins as therapeutics. He is a member of many professional societies and associations, and serves as a referee for several international journals. Dr Knop was awarded his medical degrees from the University of Copenhagen.

Tina Vilsbøll is a Physician at the Gentofte Hospital, Steno Diabetes Centre and Herlev Hospital, University of Copenhagen. She has extensive specialist training in clinical endocrinology. Her research focuses on the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) and their role in type 2 diabetes. She has been awarded several grants for her research from various organisations and serves as peer reviewer for several journals. Dr Vilsbøll received her MD from the University of Copenhagen in 1995.

subjects).[25] In the majority of patients with type 2 diabetes, the reduced incretin effect is accompanied by a moderate degree of GLP-1 hyposecretion (a reduction of approximately 15%)[26] and a weakened insulinotropic potency of GLP-1 at physiological concentrations, although at supraphysiological doses GLP-1 is able to elicit robust insulin responses in patients with type 2 diabetes.[27] As opposed to GLP-1, GIP is secreted normally or even hypersecreted in patients with type 2 diabetes.[28] However, beta-cell responsiveness to GIP is greatly reduced with an almost complete loss of late-phase insulin secretion in response to even supraphysiological doses.[29]

Theoretically, changes in plasma DPP-4 activity and/or the elimination rates of the incretin hormones could contribute to the reduced incretin effect in patients with type 2 diabetes; however, such differences have not been found to exist between patients with type 2 diabetes and healthy control subjects. It is assumed that the incretin-related deficiencies could contribute to the inability of type 2 diabetes patients to adjust their insulin secretion to their needs. The molecular mechanisms underlying the reduced incretin effect, the affected beta-cell sensitivity to GLP-1 and the near loss of the insulinotropic effect of GIP are currently unknown. However, recent data indicate that the incretin-related deficits are consequences of the diabetic state (and/or insulin-resistant state) rather than primary pathogenetic factors,[30–32] implying that it may be possible to correct these deficiencies through intervention. Accordingly, physicians have recently been armed with new antidiabetic drugs based on incretin hormones, adding to the arsenal of existing treatment modalities aimed at controlling glucose homeostasis in type 2 diabetes.

### *Current Treatment Modalities*

The aim of diabetic treatment is to control the glucose homeostasis as tightly as possible to prevent the risk of macro- and microvascular complications and early death, without adverse effects such as hypoglycaemia. With the revision to the 2008 clinical practice recommendation, the glycated haemoglobin ($HbA_{1c}$) goal for non-pregnant adults in general is below 7%, and for selected individuals below 6%.[33] Because of the complex nature of the disease, glycaemic control remains difficult and often requires several antidiabetic drugs in addition to lifestyle interventions (exercise, diet, weight control). Even when the disease is being fought in an optimal interdisciplinary setting with a maximum polypharmaceutical approach, the recommended goals are difficult to achieve. This is partly due to the fact that type 2 diabetes is a progressive disease with an almost linear decline in beta-cell function (probably combined with a decrease in beta-cell mass) over time.

The pre-existing oral antidiabetic drugs reduce blood sugar levels by different mechanisms. Biguanides (e.g. metformin) decrease hepatic glucose production, decrease intestinal glucose absorption and increase glucose uptake by skeletal muscle and fat. Sulphonylureas (e.g. glimeperide) and glinides stimulate pancreatic insulin secretion. Thiazolidinediones decrease hepatic glucose output and increase insulin-dependent glucose uptake in skeletal muscle and fat. Alpha-glucosidase inhibitors inhibit pancreatic alpha-amylase and membrane-bound alpha-glucosidase enzymes and prevent intestinal disaccharide metabolism, thereby reducing glucose utilisation and absorption from ingested carbohydrates. Despite the relatively broad range of different targets within the existing types of oral antidiabetic therapies, a number of shortcomings are associated with them – even when they are used in combination. These include inadequate efficiency in glucose lowering, limited durability of glycaemic response, inconvenient dosing regimens and safety and tolerability issues. The most common adverse effects are gastrointestinal discomfort (especially with biguanide and alpha-glucosidase inhibitors), weight gain (especially with sulphonylureas and thiazolidinediones), hypoglycaemia (sulphonylureas) and elevated liver enzymes (thiazolidinediones, alpha-glucosidase inhibitors).[34] None of the above-mentioned oral antidiabetic drugs has been shown to preserve pancreatic beta-cell function over time and, notably, sulphonylureas have been shown to accelerate the apoptosis of the human beta-cells.[35] Supplementation of endogenous insulin secretion with subcutaneous (SC) injections of insulin or insulin analogues may be necessary in patients with long-standing type 2 diabetes in order to compensate for their insulin deficiency. The major side effects of insulin treatment are weight gain and risk of hypoglycaemia.

The limitations of the pre-existing antidiabetic treatment modalities as outlined above make new medical therapies that offer improved efficacy and/or durability, better convenience and an improved safety and tolerability profile absolutely imperative in order to get more patients to glycaemic goal initially and to avoid or delay the need for additional treatment.

### *Glucagon-like-peptide-1-based Therapy*

In 1993 Nauck et al. demonstrated that a four-hour continuous IV infusion of native GLP-1 is capable of normalising blood glucose concentrations in patients with type 2 diabetes.[36] However, as a safe, reliable and compliant method of delivery, IV infusions are clearly not of any clinical utility. Next, in 2002 Zander et al. demonstrated that six weeks of continuous SC infusion of native GLP-1 (using an insulin pump) in patients with type 2 diabetes significantly decreased $HbA_{1c}$ and bodyweight and greatly improved the first-phase insulin response and maximal beta-cell secretory capacity.[37] However, an important limitation to administration of the native hormone is the short half-life of native GLP-1, making it unsuitable as a therapeutic agent for the treatment of type 2 diabetes.[38,39] Therefore, in order to exploit the beneficial actions of the hormone, long-acting stable analogues of GLP-1 – the so-called incretin mimetics – and orally available inhibitors of DPP-4, the enzyme responsible for the rapid degradation of GLP-1 and GIP – the so-called incretin enhancers – have been developed. Below, key points regarding the efficacy, safety and tolerability of the currently available incretin-based strategies will be dealt with in order to accommodate the positioning of incretin-based treatments within an optimal management regimen for type 2 diabetes.

### *Incretin Mimetics*

GLP-1 analogues are agonists for the GLP-1 receptor and take advantage of the physiological actions of GLP-1. Thus, during treatment with these drugs both alpha- and beta-cell dysfunction are targeted, i.e. not only is glucose-induced insulin secretion enhanced, but also the disrupted insulin:glucagon ratio is improved. Furthermore, these drugs elicit the same effects on food intake and bodyweight as native GLP-1, treating one of the presumed cornerstones of type 2 diabetes – namely obesity. Lastly, it is hoped that the beta-cell-protective and beta-cell-trophic effects of the GLP-1 analogues, as observed in animal studies, will target the progressive structural and

functional beta-cell deterioration of type 2 diabetes and lead to improvements in long-term pancreatic islet health.

Currently, many GLP-1 analogues are under clinical development, but so far only one drug has been introduced to the market: exenatide (Byetta®). Exenatide was isolated from the venom of the lizard *Heloderma suspectum* in a search for biologically active peptides.[40] Exenatide shares only 53% homology with native GLP-1, but is equipotent and binds to and activates GLP-1 receptors on pancreatic beta-cells, following which insulin secretion and synthesis are initiated.[41] Unlike native GLP-1, exenatide is not substantially degraded by DPP-4, but is cleared primarily in the kidneys by glomerular filtration,[42] resulting in a plasma half-life for the peptide of approximately 30 minutes after IV administration.[43] After SC injection of the maximally tolerated dose, the half-life is approximately two hours, and a significant elevation of exenatide in plasma may be observed for five to six hours, but is negligible after 12 hours post-dose; this means that twice-daily doses are needed in order to obtain clinically significant effects on glycaemic control.[44]

Combining data from studies comparing GLP-1 analogues with placebo injections showed a statistically significant difference in $HbA_{1c}$ (approximately 1%) from baseline in favour of the GLP-1 analogues.[45] Addition of exenatide to existing therapy (metformin or sulphonylurea) shows substantial benefits,[46] with a 1.1% reduction in $HbA_{1c}$ after 26 weeks and a 2.3kg reduction in bodyweight compared with baseline. In an open-label extension of the study (three years), sustained effects were demonstrated with respect to glycaemic control and bodyweight, with a 1% decrease in $HbA_{1c}$ and a 5.3kg reduction in bodyweight. An important limitation of the study, in addition to its open-label design, was the high drop-out rate due to adverse events, loss of glucose control, patient/investigator decision or protocol violation, with only 217 subjects completing the study (three years) out of 517 randomised subjects.

Exenatide treatment has been compared with insulin glargine or biphasic insulin aspart, and after one year of treatment similar glycaemic control was obtained.[47,48] In contrast to insulin therapy, treatment with exenatide resulted in clinically relevant reductions in post-prandial glycaemia and bodyweight after one year (bodyweight difference of more than 5kg).[49] The major adverse effects of exenatide include mild to moderate nausea and vomiting; both seem to decline over time. Exenatide treatment is associated with a low risk of hypoglycaemia, apparently because of the glucose-dependent effect of GLP-1 on insulin secretion. However, when combined with sulphonylurea the risk of hypoglycaemia appears to be increased and to be dependent on the dose of sulphonylurea.

Exenatide is recommended as an add-on treatment to patients with type 2 diabetes who cannot achieve adequate glycaemic control on maximum tolerated doses of metformin and/or sulphonylureas. It is given by SC injections twice a day, starting with a dose of 5µg and increasing up to 10µg. Exenatide should not be used in patients with kidney failure.[50]

### *Incretin Enhancers*

The antidiabetic effects of GLP-1 can also be exploited by protecting endogenous GLP-1 from degradation by the enzyme DPP4.[51] Administration of inhibitors of this enzyme (incretin enhancers) increase the circulating levels of active GLP-1 and GIP, which is associated with the expected antidiabetic effects including stimulation of glucose-induced insulin secretion, inhibition of glucagon secretion and, possibly, preservation of beta-cell mass.[52] The inhibitors are small molecules that are active upon oral administration, and, as mentioned, they appear to elicit effects on insulin and glucagon secretion that are very similar to those obtained with the incretin mimetics, which all require parenteral administration.[53]

Treatment with DPP-4 inhibitors does not decrease bodyweight, in contrast to the incretin mimetics (they are bodyweight-neutral). This is presumably because the plasma concentrations of active GLP-1 are dependent on endogenous secreted GLP-1 from the L cells and, therefore, are not high enough to exert this effect.[54] Currently, two incretin enhancers are available on the market: sitagliptin (Januvia®) and vildagliptin (Galvus®). Both are administered orally, once and twice daily, respectively. Like the GLP-1 analogues, the DPP-4 inhibitors have been shown to lower $HbA_{1c}$ compared with placebo (by approximately 0.7%)[55] and reduce post-prandial and fasting glucose levels.[56] Treatment with DPP-4 inhibitors has now been prescribed to more than 4 million patients worldwide. Reported adverse effects in clinical trials and post-marketing studies are low, and close to the numbers seen during controlled trials with placebo treatment.[57]

Both compounds are recommended in combination with metformin and/or sulphonylureas or thiazolidinediones when diet and exercise plus the above-mentioned drugs do not provide adequate glycaemic control. No hypoglycaemia is associated with DPP-4 inhibitors in combination with metformin or thiazolidinediones, but when administered with a sulphonylurea compound the sulphonylurea dose may be lowered to reduce the risk of hypoglycaemia. Due to the renal clearance of the endogenous incretin hormones, sitagliptin should not be used in patients with kidney failure.[58] Vildagliptin is metabolised in the liver; therefore, it should not be given to subjects with impaired liver function, and biochemical liver parameters should be measured on a regular basis.[59]

## Conclusion and Perspectives

Most antidiabetic agents target only one aspect of the multifaceted pathophysiology of type 2 diabetes, and notably do not tackle the progressive deterioration of beta-cell function or the inappropriate glucagon secretion that accompanies type 2 diabetes. In contrast, incretin-based approaches are pleiotropic and, unlike existing therapies, both alpha- and beta-cell dysfunction are targeted. Comprehensive studies indicate that incretin-based therapies, perhaps especially because of their potential trophic effects on the pancreatic beta-cells, may halt the progression of disease that inevitably seems to accompany conventional treatment. The GLP-1-based treatments have shown significant and sustained improved glycaemic control combined with a minimised risk of hypoglycaemia – importantly, fear of hypoglycaemia is a common reason for non-compliance among diabetic patients. The incretin-based treatments have the additional benefit of weight loss (GLP-1 analogues) or sustained weight (DPP-4 inhibitors) in a patient population that is generally overweight or obese and tends to gain weight during most of the pre-existing antidiabetic treatments. The most prominent adverse effect of GLP-1 analogues is nausea, and adverse events during treatment with DPP-4 inhibitors are almost identical to those seen with treatment with

placebo. Due to their relatively short history, long-term studies on safety and efficacy are lacking, but so far the GLP-1-based therapies seem to have promising potential to become important agents in the optimal management regimen for type 2 diabetes. ■


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