Incretin Therapy as a Treatment Option for Type 2 Diabetes
A Primary Care Perspective

In this issue, Michael E. Cobble, MD interprets the key findings from this journal article and provides helpful recommendations on how the learnings may be applied in the busy Family Medicine office.
**Article Insights™ CME Series** are educational activities that provide practical pearls to the family physician (FP) on various therapeutic areas treated and managed by FPs. Each activity includes a reprint of an article that has recently been published in a specialty journal as well as a Question and Answer interview between two FPs on the important “take-away” points of the article reprint.

In this edition of **Article Insights™ CME Series**, Dr. Brunton will interview Dr. Cobble on how FPs may apply the findings in the journal article, “The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes” by Daniel J. Drucker, MD and Michael A. Nauck, MD, to better manage diabetes in their patients.

**faculty**

**Interviewer:**
Stephen A. Brunton, MD, FAAFP
Director of Faculty Development
Cabarrus Family Medicine Residency
Concord, North Carolina
Adjunct Clinical Professor
Department of Family Medicine
University of North Carolina at Chapel Hill
Chapel Hill, North Carolina

**Interviewee:**
Michael E. Cobble, MD
Canyons Medical Center
Adjunct Faculty
University of Utah School of Medicine
Salt Lake City, Utah

**learning objectives**

After reviewing this activity, the reader will be better able to:

- Describe the role of the incretin system in the pathogenesis of type 2 diabetes mellitus.
- Elucidate the pharmacology of the glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors.
- Compare the efficacy and safety of selected glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors with other glucose-lowering drugs.
- Identify patients with type 2 diabetes mellitus for whom a glucagon-like peptide-1 receptor agonist or dipeptidyl peptidase-4 inhibitor would be an appropriate treatment option.

**target audience**

Family physicians and clinicians who have an interest in treating patients with diabetes.
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Clinical Practice Recommendations for AAFP EB CME Designation
1. Practice Recommendation: Weight loss is associated with glucagon-like peptide 1 (GLP-1) agonist-exenatide injection (Byetta), especially when used concomitantly with metformin.
   Evidence-Based Source: National Guideline Clearinghouse
   Strength of Evidence: Supported by multiple randomized, double-blind, placebo-controlled clinical trials; included in current prescribing information

2. Practice Recommendation: Severe hypoglycemia (requiring assistance) was rare with GLP-1 analogues
   Website of Supporting Evidence: Page 201, column 1, paragraph 3
   Strength of Evidence: Systematic review of 29 published and unpublished randomized controlled trials. The ‘Quality of Reporting of Meta-Analyses’ guidelines were followed.

3. Practice Recommendation: Sitagliptin and vildagliptin therapy did not result in weight gain
   Evidence-Based Source: Cochrane Database of Systematic Reviews
   Website of Supporting Evidence: Cochrane Database Syst Rev 2008 Apr 16;(2):CD006739; Abstract
   Strength of Evidence: Systematic review of 25 randomized controlled trials with a duration of at least 12 weeks.

Medium
Text publication in the form of a reprint article with a corresponding question and answer analysis by physicians.

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The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes

Daniel J Drucker, Michael A Nauck

Glucagon-like peptide 1 (GLP-1) is a gut-derived incretin hormone that stimulates insulin and suppresses glucagon secretion, inhibits gastric emptying, and reduces appetite and food intake. Therapeutic approaches for enhancing incretin action include degradation-resistant GLP-1 receptor agonists (incretin mimetics), and inhibitors of dipeptidyl peptidase-4 (DPP-4) activity (incretin enhancers). Clinical trials with the incretin mimetic exenatide (two injections per day or long-acting release form once weekly) and liraglutide (one injection per day) show reductions in fasting and postprandial glucose concentrations, and haemoglobin A1c (HbA1c) (1–2%), associated with weight loss (2–5 kg). The most common adverse event associated with GLP-1 receptor agonists is mild nausea, which lessens over time. Orally administered DPP-4 inhibitors, such as sitagliptin and vildagliptin, reduce HbA1c by 0·5–1·0%, with few adverse events and no weight gain. These new classes of antidiabetic agents, and incretin mimetics and enhancers, also expand β-cell mass in preclinical studies. However, long-term clinical studies are needed to determine the benefits of targeting the incretin axis for the treatment of type 2 diabetes.

Introduction

Eating provokes the secretion of multiple gastrointestinal hormones involved in the regulation of gut motility, secretion of gastric acid and pancreatic enzymes, gall bladder contraction, and nutrient absorption. Gut hormones also facilitate the disposal of absorbed glucose through the stimulation of insulin secretion from the endocrine pancreas. The observation that enteral nutrition provided a more potent insulinotropic stimulus compared with isoglycaemic intravenous challenge led to the development of the incretin concept.1 The first incretin to be identified, glucose-dependent insulinotropic polypeptide (GIP), was purified from porcine intestinal extracts and had weak effects on gastric acid secretion but more potent insulinotropic actions in human beings.2 GIP is a 42-aminoacid hormone synthesised in duodenal and jejunal enteroendocrine K cells in the proximal small bowel.

A second incretin hormone, glucagon-like peptide-1 (GLP-1) was identified after the cloning of the cDNAs and genes encoding proglucagon (figure 1). GLP-1 exists in two circulating equipotent molecular forms, GLP-1(7-37) and GLP-1(7-36)amide, although GLP-1(7-36)amide is more abundant in the circulation after eating. Most GLP-1 is made in enteroendocrine L cells in the distal ileum and colon, but plasma levels of GLP-1, like GIP, also increase within minutes of eating. Hence a combination of endocrine and neural signals probably promote the rapid stimulation of GLP-1 secretion well before digested food transits through the gut to directly engage the L cell in the small bowel and colon. More proximally located L cells in the duodenum and jejunum have also been described; however, the precise

Search strategy and selection criteria

We searched the MEDLINE and PubMed databases (1987–2006) with the search terms “glp-1”, “glucagon”, “glucagon-like”, “gip”, “incretin”, “dipeptidyl peptidase-4”, and “diabetes”. We preferentially selected publications from the past 5 years, but did not exclude older publications that are commonly referenced or highly regarded. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant.

Figure 1: Physiology of GLP-1 secretion and action on GLP-1 receptors in different organs and tissues
contributions of the proximal and distal L cells to the early rapid increase in plasma GLP-1 remains unclear.

Plasma levels of GLP-1 are low in the fasted state, in the range of 5–10 pmol/L, and increase rapidly after eating, reaching 15–50 pmol/L. The circulating levels of intact GLP-1 and GIP decrease rapidly because of enzymatic inactivation, mainly dipeptidyl peptidase-4 (DPP-4), and renal clearance. Whether additional proteases, such as human neutral endopeptidase 24-11, are also essential determinants of GLP-1 inactivation is being investigated. Both GIP and GLP-1 contain alanine at position 2, and hence are excellent substrates for DPP-4. Indeed, DPP-4 is essential for incretin inactivation, and mice with targeted inactivation of the DPP-4 gene have raised levels of plasma GIP and GLP-1, increased insulin secretion, and reduced glucose excursion after glycaemic challenge. As a result of DPP-4 activity, intact, biologically active GLP-1 represents only 10–20% of total plasma GLP-1.

Both GIP and GLP-1 exert their actions by the engagement of structurally distinct G-protein-coupled receptors (GPCRs). The GIP receptor is predominantly expressed on islet β cells, and to a lesser extent, in adipose tissue and in the central nervous system. By contrast, the GLP-1 receptor (GLP-1R) is expressed in islet α and β cells and in peripheral tissues, including the central and peripheral nervous systems, heart, kidney, lung, and gastrointestinal tract (Figure 1). Activation of both incretin receptors on β cells leads to rapid increases in levels of cAMP and intracellular calcium, followed by insulin exocytosis, in a glucose-dependent manner. More sustained incretin receptor signalling is associated with activation of protein kinase A, induction of gene transcription, enhanced levels of insulin biosynthesis, and stimulation of β-cell proliferation. Both GLP-1R and GIP receptor activation also promote resistance to apoptosis and enhanced β-cell survival, in both rodent and human islets. Consistent with the distribution of GLP-1R expression, GLP-1 also inhibits glucagon secretion, gastric emptying, and food ingestion, and promotes enhanced glucose disposal through neural mechanisms, actions that also contribute to the control of glucoregulation. Notably, effects on glucagon secretion, like those on insulin secretory responses, are glucose-dependent, whereas counter-regulatory release of glucagon in response to hypoglycaemia is fully preserved even in the presence of pharmacological concentrations of GLP-1.

The physiological importance of endogenous GIP and GLP-1 for glucose homoeostasis has been investigated in studies with receptor antagonists, or gene-knockout mice. Acute antagonism of GIP or GLP-1 lowers insulin secretion and increases plasma glucose after glycaemic challenge in rodents. Similarly, mice with inactivating mutations in the GIP or GLP-1 receptors also have
defective glucose-stimulated insulin secretion and impaired glucose tolerance. GLP-1, but not GIP, is also essential for control of fasting glycaemia, since acute antagonism or genetic disruption of GLP-1 action leads to increased levels of fasting glucose in rodents. Furthermore, GLP-1 is essential for glucose control in human beings: studies with the antagonist exendin(9-39) show defective glucose-stimulated insulin secretion, reduced glucose clearance, increased levels of glucagon, and quicker gastric emptying after disruption of GLP-1 action.

The pleiotropic actions of GLP-1 and GIP on the control of blood glucose have fostered considerable interest in the use of these agents for the treatment of type 2 diabetes. Whereas in healthy human beings oral glucose elicits a considerably higher insulin secretory response than does intravenous glucose (even if leading to the same glycaemic increments), this incretin effect is substantially reduced or even lost in patients with type 2 diabetes. As an explanation for the acquired incretin defect, GIP but not GLP-1 shows noticeably attenuated insulinotropic action in patients with type 2 diabetes. Furthermore, those with type 2 diabetes show a small but significant reduction in meal-stimulated levels of GLP-1. Since GLP-1 action remains relatively preserved in diabetic patients, most pharmaceutical efforts directed at potentiation of incretin action for the treatment of type 2 diabetes have focused on GLP-IR agonists.

<table>
<thead>
<tr>
<th>Biological actions of incretin hormone in type 2 diabetes</th>
<th>Native GLP-1*</th>
<th>Incretin mimetics</th>
<th>DPP-4 inhibitors (eg, vildagliptin, sitagliptin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic features of type 2 diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Defective glucose-stimulated insulin secretion</td>
<td>Yes14</td>
<td>Yes15</td>
<td>Yes16</td>
</tr>
<tr>
<td>Lack of biphasic response†</td>
<td>Yes14</td>
<td>Not tested</td>
<td>Not tested</td>
</tr>
<tr>
<td>Slow insulin secretory response to meals§</td>
<td>Yes16,17</td>
<td>Yes18</td>
<td>Yes19</td>
</tr>
<tr>
<td>Reduction in or absence of incretin effect†</td>
<td>Yes17</td>
<td>Yes18</td>
<td>Not tested, but probable</td>
</tr>
<tr>
<td>Hyperglucagonaemia†</td>
<td>Yes19</td>
<td>Yes20</td>
<td>Yes21</td>
</tr>
<tr>
<td>Hypoglycaemia counter-regulation</td>
<td>Yes22</td>
<td>Yes23</td>
<td>Yes24</td>
</tr>
<tr>
<td>Reduced pancreatic β-cell insulin content</td>
<td>Yes25</td>
<td>Yes26</td>
<td>Yes27</td>
</tr>
<tr>
<td>Reduced endocrine pancreatic β-cell mass†§</td>
<td>Yes28</td>
<td>Yes29</td>
<td>Yes30</td>
</tr>
<tr>
<td>Abnormally high rate of β-cell apoptosis§</td>
<td>Yes31</td>
<td>Yes32</td>
<td>Probable33</td>
</tr>
<tr>
<td>Normal, decelerated or accelerated gastric emptying</td>
<td>Yes34</td>
<td>Yes35</td>
<td>No obvious effect</td>
</tr>
<tr>
<td>Hypercaloric energy intake/obesity‡</td>
<td>Yes36</td>
<td>Yes37</td>
<td>No weight change</td>
</tr>
</tbody>
</table>

Table: Type 2 diabetes and biological actions of GLP-1, incretin mimetics, and DPP-4 inhibitors

*GLP-1 exists as glycine-extended (7–37) and amidated form (7–36)amide, with both forms having similar properties; †Biphasic response is only seen under artificial conditions leading to rapid rise in glucose concentrations (glucose bolus injection or “squarewave stimulus” when starting hyperglycaemic clamp); As judged by improvement (normalisation) of postprandial glucose excursions; §By definition, GLP-1 and incretin mimetics replace incretin activity; ¶These actions have only been reported from animal or in vitro (eg, islet) studies, methods to assess human β-cell mass in vivo are not available; ||Hydrogen peroxide, free fatty acids, or streptozotocin.
Antidiabetic actions of GLP-1
Short-term intravenous infusions of GLP-1 (1–1.2 pmol kg\(^{-1}\) min\(^{-1}\), leading to pharmacological plasma concentrations of total GLP-1 of 70–150 pmol/L, and of intact biologically active GLP-1 of 10–20 pmol/L lowers blood glucose in patients with type 2 diabetes through a transient glucose-dependent stimulation of insulin and suppression of glucagon secretion and gastric emptying.\(^{38–40}\) A 6-week subcutaneous infusion of GLP-1 in patients with type 2 diabetes, achieving plasma levels of GLP-1 in the 60–70 pmol/L range,\(^{41}\) produced substantial improvements in insulin secretory capacity, insulin sensitivity, a reduction in HbA\(_\text{O}\), of 1–2% and modest weight loss (1–9 kg).\(^{42}\) Although intravenous or subcutaneous GLP-1 infusions could be useful for the short-term control of hyperglycaemia,\(^{43,44}\) the long-term treatment of type 2 diabetes needs a more feasible approach to achieve sustained activation of GLP-1 receptors. The efficacy of injectable GLP-1 receptor agonists (degradation-resistant peptides or larger proteins with more suitable pharmacokinetic properties, figure 2) and DPP-4 inhibitors (small molecules with good oral bioavailability, webtable),\(^{25–42}\) has been assessed in clinical trials.

GLP-1R agonists
Exenatide
Exenatide (synthetic exendin-4) was discovered in the search for biologically active peptides in lizard venom.\(^{45}\) Exendin-4 shares roughly 50% of its aminoacid sequence with mammalian GLP-1, is encoded by a unique gene in the lizard,\(^{46}\) and is a potent degradation-resistant agonist at the mammalian GLP-1R (figure 2).\(^{47}\) Exenatide has been developed for the treatment of type 2 diabetes (table).\(^{48–50}\) Exenatide has a circulating half-life of 60–90 min,\(^{51}\) with increases in plasma exenatide concentrations lasting 4–6 h after a single subcutaneous injection.\(^{52–54}\)

Phase III trials investigated the efficacy of adding exenatide (5 or 10 ìg by subcutaneous injection twice daily) to ongoing therapy in patients suboptimally controlled on oral antidiabetic agents (metformin,\(^{25}\) sulphonylureas,\(^{55}\) a combination of both,\(^{25,56}\) or thiazolidinediones\(^{57}\)). The starting dose of exenatide is 5 ìg twice daily for 4 weeks, followed by an increase to 10 ìg twice daily.\(^{58–60}\) Exenatide reduced HbA\(_\text{O}\), concentrations by 0–8–1–0% (figure 3)\(^{61–64}\) over 30 weeks, with prevention of weight gain or modest weight loss of 1–5–3 kg. Patients continuing in an open-label extension lost more weight, with the total weight loss reaching 4–5 kg after 80 weeks.\(^{59}\) The commonest adverse events with exenatide were gastrointestinal (nausea, or more rarely vomiting or diarrhoea)\(^{65–67}\) (figure 3). However, exenatide was rarely discontinued because of side-effects, and the occurrence of nausea lessened the longer the duration of therapy.\(^{68–70}\) An increased number of mild to moderate hypoglycaemic events was noted in patients given exenatide and sulphonylureas,\(^{71–74}\) but not in those given exenatide and metformin,\(^{75}\) despite a similar reduction in glycaemia.

40–50% of patients receiving exenatide develop antibodies with weak binding affinity and low titres.\(^{76–78}\) Antibody formation has not been associated with impaired antidiabetic effectiveness of exenatide in most of those treated. However, the drug might not be as effective in the few patients with high-titre antibodies.

Exenatide has been compared with insulin glargine in an open-label study as additional treatment for diabetic patients not achieving effective glucose control on metformin and a sulphonylurea.\(^{29}\) Fasting glucose concentrations were reduced more in patients receiving insulin glargine, but postprandial glucose reduction was greater with exenatide, especially after breakfast and dinner. Both exenatide and insulin glargine reduced levels of HbA\(_\text{O}\), by 1–1% over 26 weeks.\(^{29}\) No significant differences in overall rates of hypoglycaemia were seen in the different treatment groups, although nocturnal hypoglycaemia was less frequent with exenatide and daytime hypoglycaemia was less common in patients given insulin glargine. Gastrointestinal side-effects, such as nausea and vomiting, were more often reported with exenatide than with insulin glargine, and the dropout rate was also higher in the exenatide-treated cohort. However, patients receiving insulin glargine gained an average of 1–8 kg compared with a 2–3 kg weight loss in exenatide-treated patients.\(^{29}\) Exenatide was approved by the US Food and Drug Administration for the treatment of type 2 diabetes in April, 2005. In Europe, exenatide is expected to be approved by the end of 2006 or early 2007 for use in patients with type 2 diabetes that is not well controlled on oral agents.

Liraglutide
Liraglutide, a partly DPP-4-resistant GLP-1 analogue, contains a Arg34Lys substitution, and a glutamic acid and 16-C free-fatty-acid addition to Lys26 (figure 2).\(^{50}\) The acyl moiety promotes non-covalent binding to albumin with 1–2% of liraglutide circulating as the non-albumin-bound free peptide.\(^{50}\) Liraglutide has a half-life of about 10–14 h after subcutaneous administration in human beings,\(^{81,82}\) and can be given as a once daily injection. Early phase II studies were done with up to 0.75 mg per day of liraglutide,\(^{83–85}\) but more recent studies with weekly escalating dose- titration have investigated the efficacy of doses up to 2.0 mg.\(^{86}\) Liraglutide reduces fasting and postprandial glucose, and levels of HbA\(_\text{O}\), by up to 1–75% (figure 3),\(^{87}\) while preventing weight gain or inducing modest but significant weight loss.\(^{88–90}\) Nausea, vomiting, and diarrhoea were the most prominent adverse events but were generally mild, transient, and rarely caused discontinuation of liraglutide treatment.\(^{81,91}\) So far, no studies of exposure to liraglutide have reported antibody formation, and phase III testing was started earlier this year.
Incretin mimetics DPP-4 inhibitors

Exenatide (twice daily) Exenatide LAR (once weekly) Liraglutide (once daily) Placebo
Insulin glargine Metformin Vildagliptin Glimepiride Sitagliptin Rosiglitazone

0·5 1·0 –0·5 0·0 –1·0 –1·5 –2·0 20 –20 0 –40 –60 –80 3 2 1 –1 –2 –3 –4 –5 0

100 90 80 70 60 50 40 30 20 10 0

30 15 26 15 12 5 14 12 5

100 90 80 70 60 50 40 30 20 10 0

Duration (weeks): Duration (weeks):

Metformin Sulfonylurea Metformin+sulfonylurea TZD (metformin) TZD (sulfonylurea) Metformin+TZD Metformin+OAD Metformin (washout)

50 mg 100 mg Up to 200 mg

50 mg 25 mg Up to 100 mg 100 mg

HbA1c (%) Change in fasting glucose (mg/dL) Change in bodyweight (kg) Hypoglycaemia (%) Nausea (%)

A B C D E

* Significant differences to placebo or respective comparator; if no comparator is shown, results are depicted as placebo-subtracted differences. Bars are mean and SE. OAD=oral antidiabetic agents.
Long-acting GLP-1R agonists

Because one subcutaneous injection of exenatide does not produce effective glucose control for more than 6–8 h, there is considerable interest in the development of long-acting GLP-1R agonists that need less frequent parenteral administration. Exenatide long-acting release (LAR) is a poly(lactide-glycolide) microsphere suspension containing 3% exendin-4 peptide that shows sustained dose-dependent glycaemic control in diabetic fatty Zucker rats for up to 28 days after one subcutaneous injection. Preliminary experience with exenatide LAR in 45 patients with type 2 diabetes indicates a much greater reduction in fasting glucose concentrations and HbA\(_1c\) after once weekly administrations of exenatide LAR for 15 weeks compared with exenatide twice daily. However, long-term experience with the drug in larger numbers of patients has not yet been reported. Exenatide LAR is currently being assessed in a phase III head-to-head trial against twice-daily exenatide.

Additional strategies for development of long-acting GLP-1R agonists include the use of chemical linkers to form covalent bonds between GLP-1 (CJC-1131) or exendin-4 (CJC-1134). Similarly, recombinant albumin-GGLP-1 protein has been developed that mimics the full range of GLP-1 actions in preclinical studies. Although these drugs are expected to have an extended pharmacokinetic profile suitable for once weekly dosing in diabetic patients, little clinical information is available about the efficacy and safety of these albumin-based drugs in human beings.

DPP-4 inhibitors

The observation that GLP-1 is rapidly degraded by DPP-4 has fostered the development of specific protease inhibitors that prevent the rapid fall of GLP-1 in circulating plasma after eating. DPP-4 is a ubiquitous membrane-spanning cell-surface aminopeptidase widely expressed in many tissues, such as liver, lung, kidney, intestinal brush-border membranes, lymphocytes, and endothelial cells. The extracellular domain of DPP-4 can also be cleaved from its membrane-anchored form by a rise in postprandial levels of intact GLP-1. Most published studies used vildagliptin.

Many small-molecule DPP-4 inhibitors have been developed that specifically and potently inhibit DPP-4 activity after oral administration. Typically, these agents reduce serum DPP-4 activity by more than 80%, with some inhibition maintained for 24 h after one dose or with once daily treatment. DPP-4 inhibition is accompanied by a rise in postprandial levels of intact GLP-1. Preliminary experience with exenatide LAR for up to 28 days after one subcutaneous injection. Preliminary experience with exenatide LAR in 45 patients with type 2 diabetes indicates a much greater reduction in fasting glucose concentrations and HbA\(_1c\) after once weekly administrations of exenatide LAR for 15 weeks compared with exenatide twice daily. However, long-term experience with the drug in larger numbers of patients has not yet been reported. Exenatide LAR is currently being assessed in a phase III head-to-head trial against twice-daily exenatide.

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Vildagliptin and sitagliptin

At a dose of 100 mg once daily, fasting and postprandial glucose concentrations were reduced after 4 weeks of vildagliptin treatment. Plasma glucagon concentrations were suppressed after vildagliptin treatment, together with an increase in the ratio of insulin to glucagon. In clinical studies of longer duration, the addition of vildagliptin to patients already given metformin reduced HbA\(_1c\) by 0.8% after 12 weeks, compared with placebo, and this difference was maintained during an open-label extension for 52 weeks (figure 3). Indirect evidence from modelling experiments suggests that β-cell function is improved with vildagliptin treatment over 1 year in patients with type 2 diabetes.

Preliminary reports of longer phase III clinical studies with vildagliptin monotherapy, either 50 mg twice daily or 100 mg once daily, showed sustained efficacy but slight non-inferiority compared with metformin after 1 year of therapy, although vildagliptin was better tolerated than metformin. Similarly, vildagliptin was as effective as rosiglitazone in direct comparison monotherapy study and also produced significant reductions in HbA\(_1c\) when used in combination with metformin (figure 3).

Clinical studies have also been reported for sitagliptin (figure 3). Phase III clinical trial data presented at the American Diabetes Association meeting in June, 2006, indicated that sitagliptin is well-tolerated at doses of 100 mg once daily, either as monotherapy, or in combination with metformin or pioglitazone, without significant hypoglycaemia or weight gain. Fewer data are available for other DPP-4 inhibitors in development such as saxagliptin or denagliptin. Thus whether various chemically distinct DPP-4 inhibitors will show significant differences in pharmacokinetic profiles, side-effects, or clinical activity cannot be predicted. Sitagliptin was approved for the treatment of type 2 diabetes in the USA in October, 2006.

No characteristic pattern of adverse events has been associated with the use of vildagliptin or other DPP-4 inhibitors, despite the large number of potential substrates for DPP-4. In view of the widespread expression of DPP-4 on many cell types, including lymphocytes, there is considerable interest in the long-term safety profile of DPP-4 inhibitors. Although highly selective DPP-4 inhibition seems to be well tolerated in preclinical studies and DPP-4 inhibitors do not substantially inhibit cell proliferation in experiments with human lymphocytes in vitro, considerable
additional clinical experience with these agents will be needed before any theoretical safety concerns emerge. Furthermore, given the large number of chemically distinct DPP-4 inhibitors under clinical development, it seems likely that one or more of these agents could be associated with adverse events arising as a result of unique properties attributable to the individual chemical structure, as opposed to a class effect arising as a consequence of inhibition of DPP-4 activity. Non-selectivity for actions on the related enzymes DPP-8, DPP-9, or both, could be of particular importance.106

Contrasting properties of GLP-1R agonists and DPP-4 inhibitors

Twice daily exenatide through subcutaneous injection is indicated for the treatment of patients with type 2 diabetes mellitus in whom one or more oral agents do not work, often as an alternative to insulin treatment. By contrast, once daily DPP-4 inhibitors could be used as first-line therapy, or as add-on therapy to patients failing one or more oral agents. While there does not seem to be a great difference in the HbA1c-lowering capacity of GLP-1R agonists compared with DPP-4 inhibitors, the obvious difference between these classes of drugs is their effect on bodyweight. Weight loss is a common outcome of therapy with native GLP-1,22 exenatide, 25–27 and liraglutide, 32,75 whereas treatment with DPP-4 inhibitors is associated with prevention of weight gain14,15,30,106 (figure 3). By contrast, gastrointestinal side-effects, predominantly nausea, are often reported after treatment with injectable GLP-1R agonists but have not been described with DPP-4 inhibition.16,17,30–35 These differences might be explained in part by the relatively modest stabilisation of postprandial GLP-1 seen after DPP-4 inhibition, compared with the pharmacological increases in circulating levels of GLP-1R agonists exemplified by exenatide. Hence therapy with DPP-4 inhibitors might not be associated with weight loss perhaps partly because of the relative levels of GLP-1 achieved after treatment with these agents. Although nausea is a common side-effect of exenatide therapy, many patients lose weight independently of nausea. Consistent with the above differences in circulating levels of GLP-1, GLP-1R agonists, but not DPP-4 inhibitors, greatly decelerate gastric emptying.65,30,34,106

Future developments

Liraglutide and exenatide are first-generation GLP-1 receptor agonists, requiring once or twice daily parenteral administration, respectively. Much effort continues to be directed towards improvement of the pharmacokinetic profile of GLP-1R agonists, to minimise peak levels of the drug and thus reduce the extent of nausea. Longer-acting GLP-1R agonists should ideally provide more uniform and sustained GLP-1R activation over a 24-h period, but require less frequent administration.

Furthermore, there is great interest in determining whether chronic therapy with GLP-1R agonists will be associated with sustained long-term control of HbA1c, and improvement in β-cell function beyond that achievable with existing agents. Similar questions pertain to the DPP-4 inhibitors, which also indirectly target β cells; however, long-term clinical data assessing the durability and efficacy of these agents in the treatment of type 2 diabetes are not yet available. Because patients with type 2 diabetes have increased risks of cardiovascular morbidity and mortality, the observation that GLP-1R agonists improve myocardial function in human patients after myocardial infarction109 highlights the need for studies that assess cardiovascular endpoints in patients treated with DPP-4 inhibitors or GLP-1R agonists. Overall, agents that enhance incretin action show great promise for the treatment of type 2 diabetes by recruitment of new, often physiologically based mechanisms of action for glucoregulation, in the context of a currently favourable safety profile. Nevertheless, long-term clinical studies are needed to compare these agents with existing oral therapies or insulin, or both, to permit a greater understanding of the true benefits and role of these drugs for the treatment of diabetes mellitus.

Conflict of interest statement

D J Drucker is an inventor or co-inventor on patents related to the field of type 2 diabetes that are licensed to Amylin Pharmaceuticals Inc or Arisaph Pharmaceuticals Inc. He has served as a consultant or adviser within the past 12 months to Abbott Laboratories, Amgen Inc, Amylin Pharmaceuticals, Bayer Inc, Chugai Inc, ConjuChem Inc, Eli-Lilly Inc, GlaxoSmithKline, Glenmark Inc, Johnson & Johnson, Merck Research Laboratories, Novartis Pharmaceuticals, NPS Pharmaceuticals Inc, PPD Inc, Takeda Inc, Transition Pharmaceuticals Inc, and Arisaph Pharmaceuticals Inc. M A Nauck has received grants for the support of product-related studies from Amylin Pharmaceuticals, Eli Lilly & Co, Novartis Pharma, and NovoNordisk and consulting honoraria from Amgen, Amylin Pharmaceuticals, Bayer, ConjuChem, Eli Lilly & Co, GlaxoSmithKline, Merck, Sharp & Dohme, Novartis Pharma, and NovoNordisk. He is a co-inventor on a patent related to the clinical use of GLP-1 that is licensed to Amylin Pharmaceuticals Inc. Neither author, nor their family members, hold stock directly or indirectly in any of these companies.

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CME Series: volume 3
Incretin Therapy as a Treatment Option for Type 2 Diabetes
A Primary Care Perspective

In this third issue of Article Insights, Michael E. Cobble, MD, expands on the article by Drucker et al providing his insight into the clinical implications for primary care providers.

Question 1
Dr. Brunton: We’ve learned a lot in the last decade or so about the pathogenesis of type 2 diabetes mellitus (T2DM). Perhaps one of the most important is that insulin resistance isn’t the only mechanism involved.

Dr. Cobble: Yes, in fact, we’ve learned that there are at least 2 other mechanisms that are important. One is that pancreatic β-cell dysfunction plays a key role. The United Kingdom Prospective Diabetes Study (UKPDS) showed that an average of 50% of β-cell function remains at the time of diagnosis of T2DM, with continued decline over time. This is like driving a 6-cylinder car with only 3-cylinders operating. Recent evidence from the ACT NOW trial suggests that even less β-cell function may remain at the time of diagnosis—perhaps only about 20%. (1) This decline in β-cell function over the course of T2DM likely contributes to the diminishing efficacy of sulfonylureas and other secretagogues over time and emphasizes the importance of utilizing treatments that preserve β-cell function.

The second mechanism that’s important involves the incretin system. The existence of the incretin system was first noted back in the mid-1960s when it was observed that enteral nutrition provided a more potent insulinotropic stimulus compared with an isoglycemic challenge administered intravenously.

Question 2
Dr. Brunton: Determining that the incretin system plays a key role in the pathogenesis of T2DM has important treatment implications, doesn’t it?

Dr. Cobble: Yes, because all of the agents that we’ve had available for some time have some limitation associated with their use. For example, most oral agents have shown A1C reductions of 0.5% to 1.8%, with greater reductions typically occurring with a higher baseline A1C. Insulin lowers A1C in a dose-dependent manner with tolerability being a main issue. Sulfonylurea agents are associated with significant hypoglycemia and weight gain and they do not preserve β-cell function. Metformin is associated with adverse gastrointestinal (GI) events and no preservation of β-cell function. Glinides show insulin secretion benefits in a meal-dependent fashion, but require frequent dosing. Alpha-glucosidase inhibitors also cause adverse GI events and require frequent dosing. Thiazolidinediones are associated with fluid retention and weight gain and are contraindicated in stage 3 or 4 heart failure. Insulin promotes weight gain, causes hypoglycemia, and presents compliance issues. In addition, no agent currently approved by the US Food and Drug Administration has a mortality reduction indication, although one meta-analysis suggests that metformin may reduce all-cause mortality in patients with diabetes and heart failure. (2) Most importantly, most patients with T2DM will require more than one class of agent to achieve adequate glucose control, ie, insulin sensitizer and insulin or secretagogue. And now we can add incretin hormone therapy.
**Question 3**
**Dr. Brunton:** Would you please review the incretin system?

**Dr. Cobble:** The incretin system involves gut hormones that are secreted in response to eating. There are 2 primary incretin hormones: glucose-dependent insulino tropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1). GIP receptors are found primarily on islet β-cells, with some in adipose tissue and in the central nervous system. GLP-1 receptors are found on islet α and β-cells, as well as in the central and peripheral nervous systems, heart, kidney, lung, and GI tract.

**Question 4**
**Dr. Brunton:** What is the importance of GIP and GLP-1 in T2DM?

**Dr. Cobble:** In people with T2DM, the incretin effect is substantially reduced or lost. The release of GLP-1 in response to eating is reduced and the insulinotropic action of GIP—but not GLP-1—is noticeably attenuated. For this reason, and the fact that GLP-1 possesses other actions important in T2DM, the use of GLP-1 in T2DM has been extensively investigated. These investigations show that GLP-1 acts in a glucose-dependent manner. When blood glucose levels are elevated, GLP-1 stimulates β-cells to release insulin. GLP-1 also inhibits glucagon, which is especially important since glucagon secretion is often elevated during hyperglycemia in T2DM. As blood glucose begins to fall below normal, GLP-1 allows glucagon secretion, thereby protecting against hypoglycemia. In addition, GLP-1 slows gastric emptying and promotes early satiety, which is especially important in overweight patients with T2DM. Thus, having appropriate levels of functional GLP-1 is very important for glucose homeostasis.

**Question 5**
**Dr. Brunton:** What else have we learned from investigations of GLP-1?

**Dr. Cobble:** We have found that the effects of GLP-1 are transient because of the rapid inactivation of GLP-1 by the enzyme dipeptidyl peptidase-4 (DPP-4). As a result, the elimination half-life of GLP-1 in vivo is about 2 minutes. This has been overcome in two ways. First, GLP-1 receptor agonists or incretin mimetics have been developed that are resistant to DPP-4. Second, inhibitors have been developed that block the enzymatic action of DPP-4, thereby prolonging the action of GLP-1. These are called DPP-4 inhibitors or incretin enhancers.

**Question 6**
**Dr. Brunton:** Do the GLP-1 analogs or the DPP-4 inhibitors have any effect on the diminishing pancreatic β-cell function that is so important in the pathogenesis of T2DM?

**Dr. Cobble:** Yes, this may be the most exciting attribute of these agents. While further study is needed because most studies have been in animal models or in vitro, the GLP-1 receptor agonists enhance β-cell function, stimulate β-cell proliferation which increases mass, and promote resistance to apoptosis, thereby prolonging β-cell survival. Although less well investigated, similar benefits are observed with the DPP-4 inhibitors.

**Question 7**
**Dr. Brunton:** Let’s turn our focus to the clinical use of the GLP-1 receptor agonists and DPP-4 inhibitors in the treatment of patients with T2DM. First of all, please list the drugs we’re going to discuss.

**Dr. Cobble:** With respect to the GLP-1 receptor agonists, exenatide (Byetta) is the only one commercially available in the US. Liraglutide and exenatide LAR are currently under review by the US FDA. With respect to the DPP-4 inhibitors, sitagliptin (Januvia) is the only one commercially available. Alogliptin and vildagliptin are currently under review by the US FDA. Saxagliptin is in phase III clinical trials.
Question 8
Dr. Brunton: Although there are no published head-to-head clinical trials, what has been learned from clinical trials of the GLP-1 receptor agonists and DPP-4 inhibitors?

Dr. Cobble: They have confirmed the findings observed with GLP-1 in animal and in vitro models. That is, both the GLP-1 receptor agonists and DPP-4 inhibitors increase the secretion of insulin and decrease the secretion of glucagon, both in a glucose-dependent manner. (5,9-12) As I previously noted, an increase in B-cell mass and function is observed as well. The GLP-1 receptor agonists have the added benefit of slowing gastric emptying and decreasing the time to satiety as well as food intake. (13) The increase in satiety achieved with the GLP-1 receptor agonists results from their providing supraphysiologic levels of GLP-1 compared with the DPP-4 inhibitors, which restore the concentration of GLP-1 to a physiologic level. While not yet published, data are beginning to emerge showing that these differences between the GLP-1 receptor agonists and DPP-4 inhibitors are clinically important. A double-blind cross-over trial found that while the reduction in fasting plasma glucose from baseline was comparable after 2 weeks of exenatide or sitagliptin (14 vs 20 mg/dL, respectively; P=NS), exenatide significantly reduced the 2-hour postprandial glucose excursion (31 mg/dL from pre-prandial) compared with an increase of 47 mg/dL for sitagliptin (P<0.0001). (14) In addition, when sitagliptin patients were crossed over to exenatide, postprandial glucose was further reduced, while patients switched from exenatide to sitagliptin experienced an increase.

Question 9
Dr. Brunton: While there has been no head-to-head comparison of exenatide with liraglutide, how effective are the GLP-1 receptor agonists in treating patients with T2DM?

Dr. Cobble: In the treatment of patients with T2DM, both exenatide and liraglutide have been investigated in drug-naïve patients, as well as those who did not achieve acceptable glycemic control with other agents. As monotherapy and in combination with other agents, both drugs lower fasting and postprandial glucose leading to a reduction in the A1C level that ranges from approximately 0.5% to 1.0% for exenatide (15,16) and 0.5% to 1.6% for liraglutide. (11,17,18) Again, greater reduction in the A1C occurs with a higher baseline A1C.

An important benefit of the GLP-1 receptor agonists is their ability to promote weight loss, especially in combination with metformin. The weight loss is generally 3-4 kg with exenatide or liraglutide. (11,15-17) This benefit is critically important in many patients with T2DM.

Question 10
Dr. Brunton: What other differences are there between exenatide and liraglutide?

Dr. Cobble: While both drugs are administered subcutaneously, exenatide has a mean elimination half-life of about 2 hours compared to 13 hours for liraglutide. Consequently, exenatide must be administered twice daily prior to a meal and liraglutide once daily without regard to a meal. Both drugs affect non-glucose endpoints. Exenatide reduces systolic and diastolic blood pressure up to 6.3 and 4.1 mm Hg, respectively. (16,19) Liraglutide significantly reduces systolic blood pressure (up to 8 mm Hg), while diastolic blood pressure is lowered 1-2 mm Hg. (11,20) In addition, exenatide and liraglutide lower total and LDL-cholesterol and raise HDL-cholesterol. The greatest reduction is in triglycerides with up to a 26% reduction with exenatide (16,19) and up to 22% with liraglutide. (11)
**Question 11**  
**Dr. Brunton:** How well tolerated are exenatide and liraglutide?

**Dr. Cobble:** Both are well tolerated with adverse events generally of mild or moderate severity. As monotherapy, minor hypoglycemia occurs in 5% of patients treated with exenatide (21) and up to 12% with liraglutide, although the risk increases when a sulfonylurea is included in the regimen. (17) Severe hypoglycemia that requires assistance occurs rarely.

Nausea and vomiting are common occurring in up to 57% of patients treated with exenatide monotherapy (22) and up to 29% with liraglutide. (17) Should nausea be a significant problem, the dose of the GLP-1 receptor agonist can be cut in half. So if the dose is 5 mcg twice daily, 5 mcg once daily can be given or if the dose is 10 mcg twice daily, 5 mcg twice daily can be given. This dose should be continued for 2 weeks or so until tolerability improves. Alternatively, the GLP-1 receptor agonist can be administered during or near the end (but not after) the meal. The downside to this approach is that the benefits of early insulin secretion and glucagon suppression are lost. In addition, the satiety effect may be reduced or lost. Exenatide is not recommended in patients with a creatinine clearance less than 30 ml/minute.

Finally, probably because liraglutide is 97% homologous to native GLP-1 compared with approximately 50% for exenatide, antibody production with liraglutide is much less common. The clinical significance of this is unknown.

**Question 12**  
**Dr. Brunton:** With respect to the efficacy of the DPP-4 inhibitors, what have the clinical trials shown?

**Dr. Cobble:** Sitagliptin and vildagliptin are the best studied of the DPP-4 inhibitors involving drug-naïve patients, as well as those who did not achieve acceptable glycemic control with other agents. Although there has been no direct comparison of the DPP-4 inhibitors, experience to date with alogliptin and saxagliptin suggests roughly similar efficacy to sitagliptin and vildagliptin.

As monotherapy and in combination with other agents, sitagliptin and vildagliptin significantly lower fasting and postprandial glucose generally leading to a reduction in the A1C level of 0.5-0.8%. (12,23-27) The DPP-4 inhibitors are weight neutral or cause slight weight gain.

**Question 13**  
**Dr. Brunton:** Are there any other efficacy differences among the DPP-4 inhibitors?

**Dr. Cobble:** Sitagliptin and vildagliptin have been shown to lower total and LDL-cholesterol and triglycerides, and raise HDL-cholesterol. The greatest change is up to a 17% decrease in the triglyceride level with sitagliptin (12) and up to a 16% decrease in the LDL-cholesterol level with vildagliptin. (25)

**Question 14**  
**Dr. Brunton:** How well tolerated are the DPP-4 inhibitors?

**Dr. Cobble:** Results of clinical trials indicate that the DPP-4 inhibitors are generally well tolerated with the suggestion that the side effect profile was similar to placebo. (12,23-27) However, there have been postmarketing reports of sitagliptin causing serious hypersensitivity reactions (anaphylaxis, angioedema, and exfoliative skin conditions) within the first 3 months of therapy, even as early as the first dose. (28) In addition, concerns about adverse skin events and elevated liver enzymes have been raised by the US FDA during its review of vildagliptin. (29) Finally, the dose of sitagliptin should be reduced in patients with renal dysfunction. (28)
Question 15
Dr. Brunton: How do you use the GLP-1 receptor agonists and DPP-4 inhibitors in your practice?

Dr. Cobble: I like using the GLP-1 receptor agonists and DPP-4 inhibitors in many settings because of their unique mechanisms of action. This includes monotherapy and combination therapy, especially where preservation of β-cell function is still possible. My personal preference is to use a GLP-1 receptor agonist when substantial reduction in the A1C is needed, such as a patient with T2DM who has not achieved glycemic control with lifestyle management with or without drug therapy. It also includes a patient with an A1C above 8%, as well as in the 7% to 8% range despite maximum dose metformin. Because they promote weight loss, I use the GLP-1 receptor agonists in overweight and obese patients with T2DM, particularly those with delayed satiety. They also can be used in patients with moderate—but not severe—renal dysfunction.

I like to use a DPP-4 inhibitor instead of a GLP-1 receptor agonist for a patient where an injection is to be avoided, such as someone with needle phobia. I also use a DPP-4 inhibitor in a person with normal weight where the weight reduction benefit of a GLP-1 receptor agonist is not needed. Finally, a GLP-1 receptor agonist or DPP-4 inhibitor is an attractive option for a patient with T2DM who also has hyperlipidemia or essential hypertension, although I don’t use them in place of primary therapies that have shown to improve mortality and other related endpoints for these conditions.

Question 16
Dr. Brunton: What are the key points primary care physicians should remember about the incretin hormones, especially the major clinical differences between the GLP-1 receptor agonists and DPP-4 inhibitors?

Dr. Cobble: We have come to understand that the incretin system plays an important role in glucose homeostasis and in regulating β-cell function. Direct comparison of the GLP-1 receptor agonists and DPP-4 inhibitors is not yet possible because of different trial designs and the lack of published head-to-head trials. It does appear, however, that the GLP-1 receptor agonists cause greater lowering of the A1C level, generally in the range of 0.5% to 1.6% compared with 0.5% to 0.9% for the DPP-4 inhibitors. The reduction of the A1C is usually greater with a higher baseline A1C. (11,12,15,18,23-27) The GLP-1 receptor agonists also promote weight loss, perhaps because they increase satiety and reduce food intake (11,15-17), while the DPP-4 inhibitors are generally weight neutral. (12,24,26,30) Both groups of drugs are well tolerated, with a low incidence of symptomatic hypoglycemia. (17,21) The GLP-1 receptor agonists, but not the DPP-4 inhibitors, frequently cause gastrointestinal symptoms, although the symptoms are generally transient and easily managed. (17,22) Acute pancreatitis is rarely observed with exenatide, although some fatalities have resulted. (31) Serious allergic and hypersensitivity reactions have been reported with sitagliptin (28) and adverse skin events and elevated liver enzymes have been reported with vildagliptin. (29) The DPP-4 inhibitors are administered orally and the GLP-1 receptor agonists subcutaneously. The dose of a sulfonylurea agent is recommended to be reduced when used in combination with a GLP-1 receptor agonist (31) or DPP-4 inhibitor. (28) This may not be necessary if the A1C is 10% or above.

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