Incretin Physiology and Its Role in Type 2 Diabetes Mellitus

Frank Svec, MD, PhD

Incretins are hormones that are released after ingestion of a meal and augment the secretion of insulin. Current research suggests that GLP-1 (glucagon-like peptide 1) is the most important. Their action is terminated by enzymes known as dipeptidyl peptidase-4 (DPP-4). The observation that the incretin response may be diminished in individuals with type 2 diabetes mellitus has led to advances in the management of this disease. Agents that act as incretin mimetics, such as exenatide and liraglutide, and DPP-4 inhibitors, such as sitagliptin phosphate and saxagliptin, improve glycated hemoglobin levels either as monotherapy or in combination with other agents. Importantly, these agents either lead to weight loss or are weight neutral and are associated with a low risk of hypoglycemia—properties that further contribute to their clinical utility.

The Incretin Effect

Insulin

The presence of incretins was revealed by comparing responses of c-peptide to an oral glucose load with a comparable intravenous glucose challenge. The amount of c-peptide released in response to the oral glucose load was higher than that released in response to the intravenous glucose. Ultimately, the signal for this release was attributed to incretins—molecules that act as sensors of caloric intake in the gut and increase the release of insulin when food is ingested.

Two primary incretins have now been identified. One is glucagon-like peptide-1 (GLP-1), which is synthesized and released from L cells of the ileum. The other incretin is glucose-dependent insulinotropic polypeptide (GIP), which is synthesized and released from K cells of the jejunum. The primary site of action of GIP is the pancreatic β cells, but GIP also acts on adipocytes. The actions of both are receptor-mediated. It is currently thought that glucagon-like peptide-1 is responsible for most of the incretin effect, which is robust in people who do not have diabetes but is blunted in people with T2DM. Thus, a new therapeutic...

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window that uses GLP-1 as a way of increasing insulin secretion has been identified.

This approach was tested in a Europe-based study in which volunteers with T2DM were studied on two different days. On both days they fasted throughout the study. On one day, they received an infusion of saline, and on the other day, they received an infusion of GLP-1. As they fasted on the placebo day, their blood glucose gradually decreased. On the GLP-1 infusion day, their insulin levels increased and their glucose decreased faster. These findings indicate that GLP-1 releases insulin in patients with T2DM and can lower blood glucose (Figure 1).

Unfortunately, GLP-1 has a short half-life (approximately 2 minutes) because it is rapidly attacked by the enzyme dipeptidyl peptidase-4 (DPP-4), which cleaves the last two amino acids of GLP-1. This action inactivates the molecule, making it unsuitable for therapeutic use. Fortunately, a solution was found with the discovery of exendin-4, a naturally occurring peptide that was originally isolated from the salivary secretions of the Gila monster, a poisonous lizard. While the animal’s use of this molecule is unknown, exendin-4 is structurally similar to GLP-1. Because of critical amino acid substitutions, it is resistant to DPP-4 inactivation. Importantly, exendin-4’s structure is so similar to GLP-1 that it interacts with the GLP-1 receptor and mimics its actions. This discovery led to the development of the GLP-1 mimic exenatide (synthetic exendin-4), which is commercially available and can be administered as a twice-daily injection.

Since that initial discovery, other analogues of GLP-1 have been constructed and one, liraglutide, has been brought to market. It binds to albumen through a fatty acid side chain and is metabolized slowly. As a consequence, this GLP-1 analogue needs to be injected only once a day.

**Glucagon**

Glucagon is another important hormone involved in the metabolism of carbohydrates. It acts on the liver to enhance gluconeogenesis during periods of fasting, thus preventing the development of hypoglycemia. Glucagon levels are known to increase during periods of fasting and decrease after the ingestion of a meal in patients without diabetes. In patients with T2DM, this pattern may not be seen.

In those with diabetes, glucagon levels may paradoxically rise after ingestion of a carbohydrate meal and enhance the production of glucose through gluconeogenesis. Consequently, not only are glucose levels increased due to insulin deficiency, but also more glucose is being produced in patients with diabetes after a meal. Thus, there are actually two mechanisms by which postprandial hyperglycemia occurs in patients with diabetes.

Interestingly, when patients with diabetes are given an injection of incretin-like exenatide before ingestion of the carbohydrate meal, the rise in glucagon is no longer observed (Figure 2). Thus, GLP-1 mimetics improve glucose control through two mechanisms: an increase in insulin and a decrease in glucagon.

Like the GLP-1 effect on insulin, this effect on glucagon is glucose dependent. Returning to the experiment where indi-
Individuals with diabetes fasted and received either an infusion of saline or GLP-1 (Figure 1), as the blood glucose approaches normal fasting levels, glucagon levels stopped falling and began to rise. This effect protected against hypoglycemia and demonstrated that the effects of GLP-1 on insulin and glucagon are glucose dependent. If glucose levels are high, insulin will be released and glucagon activity will decrease. As soon as the glucose levels approach normal, the actions of GLP-1 stop. This result renders GLP-1 mimetics highly valuable clinically, because their actions stop in the presence of low levels of glucose. Thus, the risk of developing hypoglycemia is extremely low.

Other Effects
Glucagon-like peptide-1 has also been shown to slow gastric digestion. This effect may be beneficial because it allows for a slower introduction of carbohydrate into the blood and allows for a better match of the delayed and diminished insulin secretion that characterizes T2DM to cover the glucose load.

Glucagon-like peptide-1 also decreases food intake through central actions that signal satiety. Infusion studies with diabetic patients have found that, over time, appetite is reduced and food intake decreases. With GLP-1, they feel satiated at the end of the meal. In practice this effect leads to weight loss.

Management of T2DM
Phase 3 trials have investigated the effect of exenatide in patients with T2DM. These trials included patients who had not reached their glycated hemoglobin (HbA1c) goals with prior therapy using oral agents. Pivotal trials used patients with T2DM who were treated with metformin, a sulfonylurea, or both metformin and a sulfonylurea. Patients who received either 5 μg or 10 μg of exenatide twice daily showed a greater decrease in HbA1c levels (Figure 3) and weight than patients treated with a placebo. The effect was sustained over 82 weeks. The difference in weight between the two groups was 7 lb, a statistically significant difference. Studies have shown that the effects of exenatide wane when treatment is terminated.

Other research has compared the efficacies of exenatide and insulin glargine as add-on therapies in patients with T2DM who have not reached their HbA1c goals with metformin, a sulfonylurea, or both. Mean baseline HbA1c levels were around 8% in patients receiving exenatide or insulin glargine. Over the 12- to 26-week treatment period, both randomly assigned groups showed comparable improvements in HbA1c, with many reaching their HbA1c goal. Importantly, patients who received insulin glargine gained weight, whereas those who received exenatide lost weight, resulting in about a 10-lb weight difference between the two agents. Thus, exenatide not only improves HbA1c levels but also favorably affects weight. Studies with liraglutide give similar results; glucose control in those taking oral agents but not at goal have improved glucose levels without gaining weight or with weight loss.

In summary, GLP-1 mimetics represent a promising new strategy for controlling diabetes. Not only do they improve HbA1c levels in patients whose diabetes is poorly controlled with metformin and a sulfonylurea, they also do not result in weight gain—an unfavorable side effect of many diabetes therapeutics.

Many other GLP-1 mimetics are in development. Some are shorter acting while others are longer acting. Results have already been presented using a long-acting release form of exenatide, which uses a once-weekly injections.
Poorly controlled diabetes.\textsuperscript{20} When added to metformin therapy in patients with type 2 diabetes, sitagliptin was compared to glipizide as a twice daily dose and then increased to 10 μg twice daily, as needed. Liraglutide is indicated for add-on therapy and is not recommended as initial therapy in patients who have not achieved adequate diabetes control on diet and exercise alone.

**Other Approaches**

Incretin enhancers are another category available for the management of T2DM. These agents, called gliptins, can inhibit the DPP-4 enzymes that degrade endogenous GLP-1 and slow the inactivation of endogenous incretins. Sitagliptin phosphate is an oral, reversible DPP-4 inhibitor that can be administered as a daily 100-mg dose or a twice daily 50-mg dose. In healthy volunteers, sitagliptin provided more than 80% inhibition of DPP-4 activity for 24 hours and increased GLP-1 plasma levels two-fold. The half life of sitagliptin is 8 to 14 hours, and it has a favorable safety profile.\textsuperscript{17,18}

Clinical trials have demonstrated that sitagliptin monotherapy significantly improved HbA\textsubscript{1c} levels over 24 weeks.\textsuperscript{19} Sitagliptin also significantly improved HbA\textsubscript{1c} levels when it was used as an add-on to metformin therapy in patients with poorly controlled diabetes.\textsuperscript{20} When sitagliptin was compared to glipizide as an add-on to metformin therapy, it was found that these agents resulted in similar reductions in HbA\textsubscript{1c} levels; however, patients assigned to glipizide gained weight, while patients assigned to sitagliptin lost a small amount of weight.\textsuperscript{21} Sitagliptin is generally considered weight-neutral.\textsuperscript{19}

Saxagliptin is another new agent that is more potent on a milligram-per-milligram basis than sitagliptin. In clinical trials, saxagliptin led to decreases in HbA\textsubscript{1c} levels when it was used in combination with metformin in patients with poorly controlled diabetes.\textsuperscript{22}

**Adverse Effects**

Adverse effects of GLP-1 therapies include nausea and other gastrointestinal side effects. These must be taken into consideration when selecting patients for therapy. The prevalence of nausea is 36% to 39% with 5-μg exenatide and 45% to 51% with 10-μg exenatide.\textsuperscript{10–12} Liraglutide also causes gastrointestinal adverse effects, though in one study,\textsuperscript{23} once-daily liraglutide caused fewer complaints than twice daily exenatide. In either case, clinical trials have shown that the longer the patient remains on either agent, the fewer the adverse effects. In both cases, prescriptions should be started using a low dose and increased slowly as tolerated.

Hypoglycemia is another side effect that must be taken into consideration. Even though there is a low risk of hypoglycemia associated with incretins by themselves, hypoglycemia can occur when a GLP-1 therapy is used in combination with an agent that is not glucose-sensitive like one of the sulfonylureas. Exenatide or liraglutide can be added to a sulfonylurea, but the dose of the sulfonylurea should be reduced initially to lessen the risk of hypoglycemia for the patient.

A GLP-1 mimic should not be used in a patient with serious documented gastroparesis, pancreatitis, or a history of medullary thyroid carcinoma. Caution should be used in those with significant renal disease and hepatic disease.

**Conclusion**

In summary, incretin-based therapies are novel agents that result in increased insulin secretion, decreased glucagon activity, delayed gastric emptying, and decreased appetite. Glucagon-like peptide-1 agonists are effective as monotherapy or add-on therapy in improving HbA\textsubscript{1c} levels. In many individuals, this approach can even lead to weight loss. Dipeptidyl peptidase-4 inhibitors enhance endogenous incretin levels and improve HbA\textsubscript{1c} levels as monotherapy or add-on therapy. These agents are generally weight-neutral.

**References**


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