

Pharmacology of GLP-1 Agonists: Describing the Therapeutic Potential to Patients

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The pathophysiology of type 2 diabetes mellitus is complex, consisting of far more physiologic defects than simple insulin resistance and β -cell dysfunction. Our understanding of this progressive disease has moved from a "dual defect" to an "ominous octet" description. This multifactorial concept may explain the difficulty in achieving and maintaining glycemic goals with traditional therapies. Glucagon-like peptide-1 (GLP-1) agonists, which improve insulin secretion, decrease glucagon secretion, increase satiety (and therefore decrease food intake), and may have beneficial effects on β -cell function, represent an important addition to treatment options. Their glucose-dependent mechanism limits the risk for hypoglycemia, and they are associated with weight loss. Glucagon-like peptide-1 agonists may be used alone in patients intolerant of metformin or in combination with metformin, thiazolidinediones, and sulfonylureas (or in any combination thereof). Concomitant use of dipeptidyl-peptidase-4 inhibitors is not recommended because they have a similar basis of action. Current US Food and Drug Administration indications do not include the concomitant use of GLP-1 agonists with insulin.

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Type 2 diabetes mellitus is a progressive metabolic disorder characterized by hyperglycemia, which arises from insufficient pancreatic insulin secretion, insulin resistance in peripheral tissues, and inadequate suppression of glucagon production. Depending on the extent of disease, antihyperglycemic therapies may be combined with lifestyle modifications (ie, nutrition and physical activity) with

the intent of delaying disease progression and improving patient outcomes.

Many patients with type 2 diabetes are failing to meet treatment goals on their current therapeutic regimens. National trend data from 2008 showed that 43% of patients with diabetes in the United States had glycated hemoglobin (HbA_{1c}) levels greater than the recommended level (ie, <7.0%).¹ Commonly used antihyperglycemic agents have several limitations, such as lack of durability and risk of hypoglycemia, which can contribute to poor glycemic control (Figure 1).² Of those patients who achieve current goals, few consistently maintain these targets over 3 years.³ The cumulative incidence of monotherapy failure at 5 years was shown to be 15% with rosiglitazone, 21% with metformin, and 34% with glyburide.² Progressive

β -cell failure also plays a major role in the lack of durable HbA_{1c} control, which may, in part, explain the high failure rate of sulfonylureas, which work to increase insulin secretion.

Concern about weight gain and hypoglycemia discourage many providers and patients from intensifying therapy.⁴ Weight gain contributes to insulin resistance and the potential risk of cardiovascular disease (CVD). Most patients gain up to 5 kg in 5 years when treated with a sulfonylurea, metformin, or a thiazolidinedione.² In the United Kingdom Prospective Diabetes Study (UKPDS), patients gained up to 8 kg over 12 years when treated with a sulfonylurea, metformin, or insulin.⁵ Further, current treatments increase the risk of hypoglycemia. Sulfonylureas, because of their mechanism of action, are the oral

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- **Weight Gain**
- **Hypoglycemia**
- **Lack of Durability**
- **Other**
 - Congestive heart failure
 - Osteoporosis

Figure 1. Limitations of traditional therapies for patients with type 2 diabetes mellitus.

agents associated with the greatest risk of hypoglycemia (up to 40% of patients in one study⁶), but data show that thiazolidinediones and metformin carry a 10% to 12% risk.²

In considering these problems with traditional diabetes medications, the present article describes the new understanding of diabetes pathophysiology and focuses on the pharmacologic basis for the use of new therapeutic options—cretin-based strategies—as an approach to glycemic control.

Update on Diabetes Pathophysiology

Diabetes has long been thought of as a disease caused by 2 primary patho-

physiologic defects: insulin resistance and insulin deficiency.⁷ In part, this belief was because available therapies primarily targeted these 2 defects. However, it is now appreciated that many more defects are present in patients with type 2 diabetes.

In his 2009 Banting lecture, Ralph DeFronzo described the “ominous octet” (Figure 2).⁷ In addition to decreased insulin secretion and decreased insulin sensitivity, DeFronzo described the influence of a decreased cretin effect, increased glucagon secretion, increased hepatic glucose production, lipolysis, glucose reabsorption by the kidney, and neurotransmitter dysfunction in the pathophysiology of type 2 diabetes. Increases in glucagon result in inadequate uptake, storage, and disposal of ingested glucose as well as elevated hepatic production of glucose leading to profound hyperglycemia.

Role of Incretins in Glucose Homeostasis

Incretins are peptide hormones secreted by entero-endocrine cells in the gastrointestinal tract. Incretins modulate pancre-

- Glucose-dependent insulin secretion
- Glucagon suppression
- Satiety
- Slowing of gastrointestinal emptying
- Improvements in β -cell function

Figure 3. Pharmacologic effects of GLP-1 agonists.

atic islet secretions as part of the “entero-insular axis,” and their primary function is to regulate postprandial nutrient utilization and storage. There are several cretin hormones, but glucagon-like peptide-1 (GLP-1) appears to be the major player in type 2 diabetes and is best understood.⁸ The primary actions are to regulate insulin and glucagon secretion only when plasma glucose exceeds normal fasting levels.⁸ Thus, a deficiency of GLP-1 is now considered as part of the pathophysiology of type 2 diabetes.⁹

The pharmacologic effects of GLP-1 are noted in Figure 3. The importance of GLP-1 is demonstrated in experiments showing that it accounts for up to 60% of

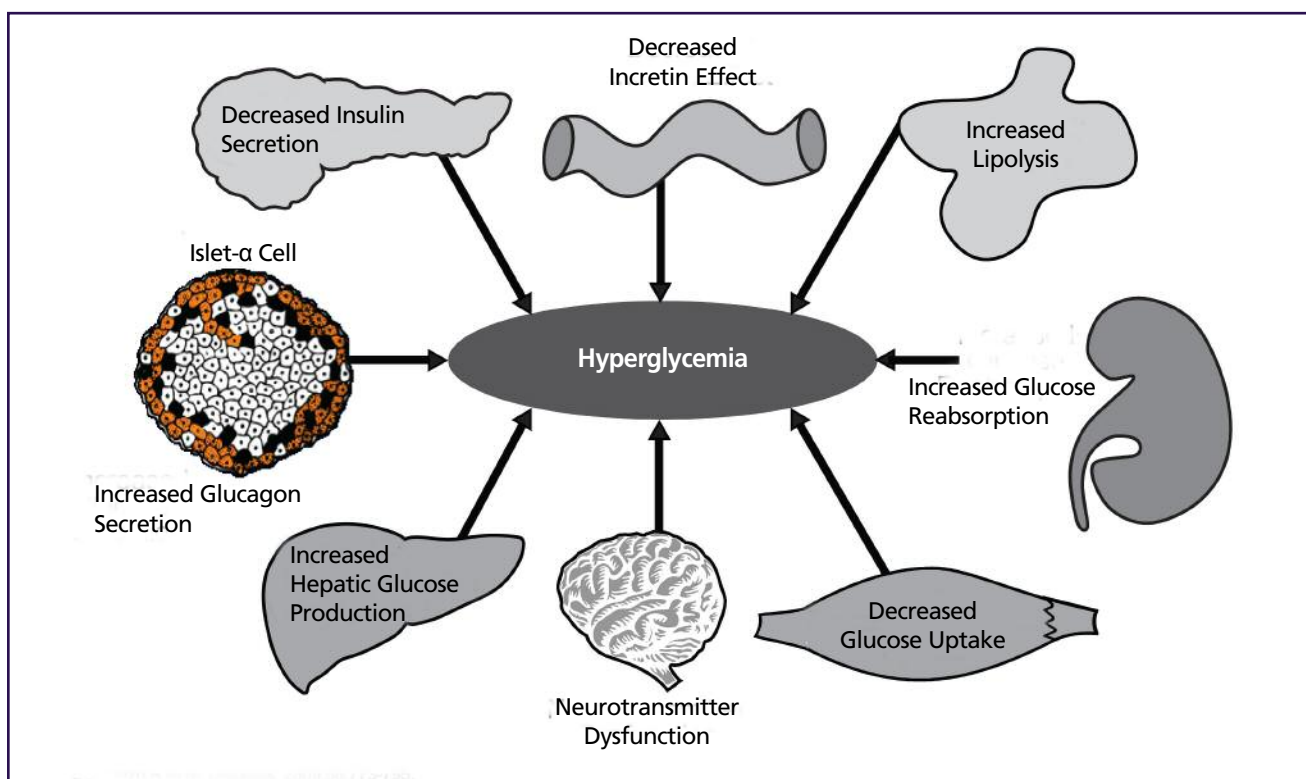


Figure 2. The “ominous octet.” Pathologic defects in patients with type 2 diabetes mellitus. Reprinted with permission from DeFronzo.⁸

Weight Loss Features

- ☐ Onset is slow (about 8 weeks) but results are progressive (continues in studies of up to 3 years duration).
- ☐ Weight loss occurs independently of gastrointestinal adverse effects. Mechanisms of action appear to be related to effects on gastric emptying and on satiety (and therefore on decreased food intake).
- ☐ Weight loss is more profound in patients with greater body mass index.
- ☐ It does not occur in all patients—some are nonresponders. Effects are not dependent on glucose change (ie, patients may have improvements in glucose levels but may not experience weight loss).

Figure 4. Weight loss features of glucagon-like peptide-1 agonists.

postprandial insulin secretion in healthy individuals.¹⁰ Glucagon-like peptide-1 analogs can be used alone or in combination with metformin, sulfonylureas, or thiazolidinediones. (As explained in the next section, GLP-1 agonists are not used in combination with dipeptidyl peptidase-4 [DPP-4] inhibitors.)

Glucagon-like peptide-1 delays gastric emptying in patients with type 2 diabetes,¹¹ thus promoting satiety and reducing food intake.^{8,12} Together, these factors may be responsible for the progressive weight loss observed with GLP-1 agonists therapy. Weight loss effects are summarized in *Figure 4*.

Strategies to Enhance Incretin Action

Strategies to correct the incretin defects in patients with type 2 diabetes include replacement of GLP-1 with a long-acting analog that resists degradation⁸ and development of drugs that inhibit the enzyme DPP-4,¹³ which breaks down GLP-1.

For the first strategy, exenatide was the first GLP-1 analog introduced for the

treatment of patients with type 2 diabetes. Liraglutide recently became available, and several other GLP-1 analogs are in development. The administration of pharmacologic quantities of GLP-1 analogs result in plasma activities that are 5- to 7-fold higher than physiologic levels. At these levels, the effects on gastric emptying, satiety, and decrease in food intake are seen. Glucagon-like peptide-1 receptor agonists induce glucose-dependent insulin secretion, β -cell protection, and other extraglycemic benefits such as weight loss and improvement in markers of cardiovascular risk. The half-life of exenatide necessitates twice-daily dosing, while the longer half-life of liraglutide allows once-daily dosing. Longer-acting GLP-1 analogs that can be administered once each month are currently in clinical trials. It appears that the longer-acting analogs are associated with lower HbA_{1c} and fasting blood glucose.¹⁴

The second strategy is aimed at enhancing the bioavailability of endogenous GLP-1. This approach focuses on inhibiting the enzyme DPP-4, which is the main enzyme that naturally breaks down GLP-1. The first DPP-4 inhibitor was sitagliptin, and saxagliptin has recently become available. Many additional DPP-4 inhibitors are in development. Dipeptidyl peptidase-4 inhibitors enable endogenous GLP-1 plasma levels to increase 2- to 3-fold, which is sufficient to increase insulin secretion and decrease glucagon secretion. Again, the effects are expressed in a glucose-depen-

dent manner. That is, a DPP-4 inhibitor can correct hyperglycemia but cannot cause hypoglycemia. Dipeptidyl peptidase-4 inhibitors do not appear to induce satiety and therefore are weight neutral. Notice that DPP-4 inhibitors are not used in conjunction with GLP-1 analogs. First, GLP-1 analogs can achieve more than 5 times the physiologic levels of GLP-1 activity, which is far greater than what can be achieved by augmenting a diminished endogenous GLP-1 response 3-fold. Second, there is no good rationale for selecting 2 therapeutic agents that target the same end biologic response.

Nonglycemic Effects of GLP-1 Agonists

There are several interesting effects of GLP-1 agonists beyond their effective glucose-lowering properties that may benefit patients with type 2 diabetes. In animals, GLP-1 agonists induce β -cell regeneration and proliferation and reduce apoptosis.^{8,15,16} The result is reconstitution of the pancreatic β -cell mass.^{8,17} In humans, therapeutic doses of GLP-1 agonists improve the capacity of β cells to sense glucose levels and respond. In fact, data demonstrate that GLP-1 agonists restore the first and second phases of insulin secretion.

It is well known that the primary cause of death for patients with type 2 diabetes is cardiovascular disease (CVD). It has long been accepted that prevention or delay of CVD emphasizes management of blood pressure and lipids in addition to normalizing blood glucose.

Human Data	Animal Data
■ β-Cell Effects ☐ Improves β-cell responsiveness ☐ Restores first-phase and second-phase insulin secretion	☐ β-cell regeneration ☐ β-cell proliferation ☐ Increases in β-cell mass ☐ Reduced apoptosis
■ Cardiac Effects ☐ Reductions in triglycerides, LDL-C ☐ Increases in HDL-C ☐ Improvements in postprandial lipid metabolism ☐ Reductions in blood pressure	☐ Increases in cardiac contractility ☐ Protection against cardiac ischemia

Figure 5. Proven effects of glucagon-like peptide-1 agonists on β cells and cardiac health according to human and animal trials.

Surprisingly, GLP-1 agonists also lower blood pressure and cholesterol¹⁸ in patients with type 2 diabetes. Reductions in systolic blood pressure have been noted within 6 weeks of therapy initiation that are beyond those associated with weight loss that can occur with the use of GLP-1 agonists.¹⁹ Improvements in triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and postprandial lipid metabolism have been observed.^{13,18,20} The cardiac benefits of GLP-1 observed in investigational models include increased cardiac contractility and protection against ischemia.^{21,22} Figure 5 summarizes the known cardiac effects of GLP-1 agonists. Other effects may still be uncovered because this is an interesting and evolving area of research.

Explaining the Therapeutic Potential to Patients

Osteopathic physicians can reinforce the usefulness of GLP-1 agonists to patients by discussing when they are indicated and when they are contraindicated. Patients with at least some pancreatic β -cell function are candidates. For these patients, the GLP-1 agonist will promote satiety, slow gastric emptying, promote weight loss, suppress glucagon secretion, increase endogenous insulin secretion, and decrease blood sugars. Glucagon-like peptide-1 agonists cannot be used in patients with absolute insulin deficiencies (ie, type 1 diabetes), and their role is diminished if diabetes is at an advanced stage. For these patients, insulin—not GLP-1—is necessary.

Perhaps one of the most important discussions to have with patients concerns safety. Glucagon-like peptide-1 agonists are associated with little or no risk of hypoglycemia. This safety issue is becoming more important as physicians recognize that hypoglycemia might be the conditioning event that triggers cardiac ischemia leading to infarction.²³ Given the multitude of metabolic defects in patients with type 2 diabetes that can be improved and the low rate of hypoglycemic events with GLP-1 agonist therapy, these agents fulfill important unmet needs in our choices of antihyperglycemic medications.

Pro	Con
■ Insulin ☐ Efficacy only limited by risk of hypoglycemia ☐ Corrects basic problem of diabetes ☐ Few drug-to-drug interactions or adverse effects other than hypoglycemia ☐ Single injection if basal insulin is used	☐ Injection ☐ Hypoglycemia risk ☐ Weight gain risk ☐ Definitive need to test and self-monitor blood glucose levels
■ Glucagon-Like Peptide-1 Agonists ☐ Glucose-dependent glucose-lowering ability ☐ Low risk of hypoglycemia ☐ Possibility of weight loss	☐ Once- or twice-daily injection ☐ Gastrointestinal adverse effects

Figure 6. Pros and cons of insulin and glucagon-like peptide-1 agonists for patients with type 2 diabetes mellitus.

Conclusion

Glucagon-like peptide-1 agonists will have substantial clinical utility for the treatment of patients with type 2 diabetes in that they target multiple defects of the disease, including those not addressed by traditional medications. In addition, they pose a low risk of hypoglycemia and have favorable effects on weight.

Case Study

A 32-year-old Hispanic woman with a 5-year history of type 2 diabetes has an HbA_{1c} of 8.1% despite combination therapy of metformin extended release, 500 mg twice daily, and glipizide extended release, 5 mg once a day.

Other medications include lisinopril, 10 mg once a day, and atorvastatin, 20 mg once a day. She is 62 inches tall and weighs 150 lbs (body mass index, 33). Blood pressure is at target (<130/80 mm Hg). At this office visit, there is discussion of poor glycemic control despite her adherence to the current therapy. The patient wants to know why more medication is needed and if she is doing something wrong (ie, if it is her fault that blood glucose levels are not staying controlled).

Often, explaining the progressive nature of the disease is helpful in teaching patients why medication therapy will need to change over time. Addition of a third oral agent is unlikely to bring this patient to goal. Treatment

options consist of adding insulin or a GLP-1 agonist. In both scenarios, it is likely that the sulfonylurea dose will need to be decreased. After discussion of the pros and cons of insulin and of the available GLP-1 agonists (Figure 6), the decision is made to start liraglutide.

Glucagon-like peptide-1 agonists are a category of antidiabetic agents with a low risk of hypoglycemia, and they are recommended for patients in whom weight gain with treatment is a concern.²⁴ The patient is told that GLP-1 agonists have many actions in treating patients with type 2 diabetes, including the ability to do the following:

- ☐ signal the pancreas to produce the right amount of insulin after eating (helps prevent blood glucose levels from escalating too high)
- ☐ stop the liver from making too much glucose when the body does not need it
- ☐ slow the rate at which food and glucose leave the stomach (helps prevent high blood glucose after eating)
- ☐ reduce appetite and therefore the amount of food eaten (many patients lose weight with these medications)

Weight loss is important in both the prevention and management of diabetes, and lifestyle interventions remain a cornerstone of therapy. With current evidence, diabetes cannot be overcome by drug therapy alone. It is important for

the patient to continue her efforts to eat healthy, nutritious meals and engage in physical activity.

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