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.
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—incretin-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 pathophysiologic 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 incretin 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 pancreatic islet secretions as part of the “enteroinsular axis,” and their primary function is to regulate postprandial nutrient utilization and storage. There are several incretin 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
postprandial insulin secretion in healthy individuals. 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, thus promoting satiety and reducing food intake. 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 degradation and development of drugs that inhibit the enzyme DPP-4, 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 HbA1c and fasting blood glucose.

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-dependent 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. The result is reconstitution of the pancreatic β-cell mass. 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.
Surprisingly, GLP-1 agonists also lower blood pressure and cholesterol\textsuperscript{18} 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.\textsuperscript{19} Improvements in triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and postprandial lipid metabolism have been observed.\textsuperscript{13,18,20} The cardiac benefits of GLP-1 observed in investigational models include increased cardiac contractility and protection against ischemia.\textsuperscript{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.\textsuperscript{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.

### 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\textsubscript{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.\textsuperscript{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.

References

Partnership to Fight Chronic Disease
The American Osteopathic Association has been an active member of the Partnership to Fight Chronic Disease (PFCD) since 2007. This supplement promotes the ideals of this partnership.

The PFCD is a national and state-based coalition of hundreds of provider, patient, community, business, and labor groups committed to raising awareness of the leading causes of death, disability, and rising healthcare costs in the United States—chronic diseases such as diabetes, asthma, cancer, and heart disease. In addition, the PFCD has worked to ensure that prevention and wellness measures were incorporated into healthcare reform legislation passed by Congress in 2010. For additional information, visit www.fightchronicdisease.org.