According to the Centers for Disease Control and Prevention’s National Diabetes Fact Sheet published in 2011, 25.8 million children and adults in the United States (8.3% of the population) have diabetes mellitus. Among these people, 18.8 million have been diagnosed as having diabetes mellitus, and 7.0 million have undiagnosed diabetes. In 2010, 1.9 million people aged 20 years or older were diagnosed as having diabetes mellitus on the basis of both fasting hemoglobin and glycosylated hemoglobin (HbA1c) criteria. The epidemic of type 2 diabetes mellitus (T2DM) in the United States and other Western countries parallels the epidemic of obesity and physical inactivity in those nations.

The importance of lowering glucose levels in patients with diabetes mellitus has been well established in several landmark studies. For example, in a 10-year follow-up of 867 patients enrolled in the United Kingdom Prospective Diabetes Study, or UKPDS, reducing fasting plasma glucose (FPG) levels below 108 mg/dL with intensive treatment provided a 25% reduction in relative risk of microvascular complications, compared with conventional treatment.

Data from the National Health and Nutrition Examination Survey (NHANES) for 1999 to 2000 suggested that only 37% of US adults with T2DM reached the established American Diabetes Association (ADA) goal of HbA1c level of less than 7%. Progress was made by the time of NHANES 2003-2004, when 52% of US adults with T2DM met the ADA’s HbA1c goal. The proportion of NHANES participants who achieved an HbA1c level of less than 7.0% was significantly lower among those receiving triple therapy (31.9%) than among those receiving metformin monotherapy (62.2%) (P < .01). These data indicate the need for new agents that will help improve glycemic control when used.

This supplement is supported by an independent educational grant from Novo Nordisk Inc.
either alone or in combination with existing agents.

The author reviews the pathophysiologic mechanisms of core defects in patients with T2DM, including mechanisms involving incretin hormones, which are peptides originating in the gastrointestinal tract that contribute to insulin secretion. The author also discusses the application of administering glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors to improve GLP-1 dynamics in patients with T2DM.

Pathophysiologic Mechanisms of Core Defects

Type 2 diabetes mellitus is a progressive disease characterized by multiple abnormalities, including insulin resistance, declines in β-cell function, and defects in α-cell function.

There are pathophysiologic abnormalities, which typically manifest before T2DM is diagnosed and continue throughout the disease process. Skeletal tissue insulin resistance, a contributor to hyperglycemia, is evident in early stages of the disease. Insulin resistance has been attributed to impaired binding of insulin to its cellular receptors and to post-binding defects, contributing to impaired glucose transport. These defects also include diminished glucose phosphorylation, impaired glycogen synthase activity, insulin signal transduction abnormalities, and decreased insulin tyrosine kinase activity.

Early in the course of T2DM, the pancreatic β cells compensate for peripheral insulin resistance by secreting more insulin. This progressive augmentation of insulin secretion by β cells eventually leads to an inability of these cells to compensate for insulin resistance. It has been estimated that as much as 80% of β cells have lost their insulin secretory function by the time of diabetes mellitus diagnosis.

The array of metabolic abnormalities contributing to the pathogenesis of T2DM—extending beyond insulin resistance and β-cell dysfunction—has been referred to as the “Ominous Octet” (Figure). For example, patients’ adipocytes demonstrate accelerated lipolysis, the kidneys increase glucose uptake and reabsorption, and the brain exhibits impaired insulin function. Patients with T2DM also have inappropriately elevated levels of glucagons, which are produced by pancreatic α cells. As a result, the liver releases excessive amounts of glucose, further contributing to hyperglycemia.

The diagnosis of T2DM is established with several hyperglycemic parameters (ie, FPG, ≥126 mg/dL; random glucose, >200 mg/dL; and HbA1c, >6.5%). Although available medications can lower levels of FPG, postprandial plasma glucose (PPG), and HbA1c, several of these agents are associated with risks of hypoglycemia and weight gain. Therefore, a need exists for exploration and implementation of newer treatments, which, on a physiologic basis, improve defects of β-cell and α-cell function, and, on a clinical basis, improve glycemic control without adverse effects.

Physiologic Effects of Incretin Hormones

An understanding of the dynamics of insulin secretion are important when evaluating new treatments such as incretin-based agents. These agents are becoming important options in the diabetes mellitus therapeutic paradigm. About 80 years ago, La Barre observed that plasma insulin levels were greater in patients with diabetes mellitus after oral ingestion of glucose, compared to intravenous infusion of comparable amounts of glucose. This difference was ascribed to the incretins, a class of gut-derived hormones. It was subsequently determined that incretins are secreted after oral ingestion of glucose but generally not after intravenous infusion of glucose. This physiologic difference was referred to as the “incretin effect.” An estimated 50% to 70% of insulin secretion can be attributed to the effects of incretins.

There are 2 major types of incretins in humans: GLP-1 and glucose-dependent insulino tropic peptide (GIP). Although GIP, which is produced by duodenal and jejunal K cells, was identified before GLP-1 as having an important impact on insulin response in patients with type 2 diabetes mellitus—referred to as the “Ominous Octet.” Adapted with permission of the American Diabetes Association, from DeFronzo RA. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus [Banting Lecture]. Diabetes. 2009;58(4):773-795; permission conveyed through Copyright Clearance Center, Inc.
Glucagon-like peptide-1 appears to be the major incretin hormone relevant to glucose homeostasis. This hormone is produced by the proglucagon gene, which is expressed in the enteronecrine L cells of the distal ileum and colon. It has a half-life of approximately 1 to 2 minutes as a result of rapid inactivation by the ubiquitous enzyme DPP-4. Glucagon-like peptide-1 increases insulin secretion from β cells in a glucose-dependent manner, ensuring appropriate insulin response after a meal. Glucagon-like peptide-1 exerts multiple actions in β cells that affect various signaling pathways and gene products. This hormone also appears to improve α-cell glucose sensing, thereby suppressing inappropriate basal and postprandial glucagon secretion.

Furthermore, GLP-1 has pleiotropic actions. It delays gastric emptying and secretion, and it promotes satiety and weight loss—as evidenced by weight loss observed with the use of GLP-1 receptor agonists. In animal models, GLP-1 induces β-cell neogenesis and proliferation and inhibits β-cell apoptosis. Therefore, GLP-1 may exert protective effects on β cells. Effects of GLP-1 on the central nervous system include enhanced memory and neuronal survival and activation of afferent pathways, which causes nausea and vomiting.

Receptors for GLP-1 are expressed throughout the cardiac system. Glucagon-like peptide-1 has been demonstrated to improve cardiovascular function after ischemia and to reduce the extent of cardiac myocyte death after experimental injury.

Type 2 diabetes mellitus results in defects in incretin secretion and action and in decreased sensitivity of β cells to GLP-1. In initial investigations, short-term intravenous GLP-1 infusions demonstrated glucose-lowering effects in patients with T2DM. Achieving supraphysiologic levels of GLP-1 through sustained subcutaneous infusions restores glucose-induced insulin secretion and elicits other beneficial effects. Modulating GLP-1 levels or activity through the production of insulin analogs or mimetics is currently a major focus of investigation. In addition, inhibition of DPP-4 is being used to increase circulating levels of GLP-1. Various properties of GLP-1 receptor agonists and DPP-4 inhibitors are shown in Table 1.

### Available and Emerging Incretin-Based Treatments GLP-1 Receptor Agonists

The development of GLP-1 receptor agonists began with the discovery of exendin-4 in the saliva of the Gila monster. Exendin-4 is 53% homologous to human GLP-1. Exenatide, the synthetic form of this compound, has been available clinically since 2005 as a twice-daily subcutaneous injection. It is indicated for use as adjunct therapy to diet and exercise, as well as monotherapy. The half-life of exenatide is 2.4 hours, necessitating twice-daily dosing before meals.

Clinical trials have established the beneficial effects of exenatide on patients’ glycemic control and body weight. The major adverse effects of exenatide are nausea and vomiting, which appear to be dose-dependent. In approximately half of the patients who receive exenatide, antibodies with weak binding affinity and low titers develop, although these antibodies do not seem to impair the antidiabetes effects of this drug.

A long-acting release (LAR) form of exenatide, exenatide LAR, has been developed by incorporating biodegradable polymeric microspheres. This once-weekly formulation is approved in Europe and is being considered by the US Food and Drug Administration (FDA). The ongoing DURATION trials are designed to assess the efficacy and safety of exenatide LAR as monotherapy and as part of combination therapy, as well as to compare it with insulin glargine and lixisenatide. Characteristics of exenatide LAR and other investigational GLP-1 receptor agonists are shown in Table 2.

The use of albumin binding to decrease the dosing frequency of GLP-1 receptor agonists has been investigated. Lixisenatide, the most recent GLP-1 agent to receive FDA approval, has 97% homologic similarity to human GLP-1 and contains a fatty acid molecule (palmitoyl) that enables it to bind to albumin. These molecular characteristics of lixisenatide limit its susceptibility to DPP-4 degradation, prolong its absorption from the injection site, and reduce its renal clearance, thereby increasing the duration of action of GLP-1. Lixisenatide has an elimination half-life of 12.6 hours, supporting once-daily dosing. Lixisenatide reduces levels of FPG, PPG, and HbA1c and induces weight loss in patients. The most common adverse effects of this drug are nausea and vomiting.

The investigational agent albiglutide was developed through the fusion of human GLP-1 (7-36) amid to recombinant human albumin, with a single amino acid substitution conferring DPP-4 resistance. Because of its prolonged half-life, albiglutide is being investigated for once-weekly administration. Furthermore, albiglutide has low permeability in the central nervous system.

<table>
<thead>
<tr>
<th>Property</th>
<th>DPP-4 Inhibitors</th>
<th>GLP-1 Receptor Agonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Currently available agents</td>
<td>Linagliptin, saxagliptin, sitagliptin</td>
<td>Exenatide, lixisenatide</td>
</tr>
<tr>
<td>Administration</td>
<td>Oral</td>
<td>Subcutaneous injection</td>
</tr>
<tr>
<td>Glucose-dependent insulin secretion</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Effects on GLP-1</td>
<td>Prevent degradation of physiologic GLP-1</td>
<td>Elevate pharmacologic levels of GLP-1</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>Minimal</td>
<td>Gastrointestinal (nausea and vomiting)</td>
</tr>
<tr>
<td>Effects on body weight</td>
<td>Neutral</td>
<td>Weight loss</td>
</tr>
</tbody>
</table>

**Abbreviations:** DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1.
bolism and is predominantly excreted in the kidneys. Dosage adjustments are required in patients with severe renal insufficiency. 27

Linagliptin is a selective, competitive DPP-4 inhibitor that the FDA approved in May 2011. 28 Linagliptin is administered orally as a single daily dose (5 mg), with no dose titration needed for patients with renal insufficiency. This xanthine-based agent is a potent, long-acting nonpeptidomimetic β-secretase inhibitor that is predominantly eliminated in feces, with minimal renal excretion compared with other DPP-4 inhibitors. 26

When used as monotherapy or in combination with metformin, DPP-4 inhibitors result in modest reductions in levels of FPG, PPG, and HbA1c, with neutral effects on body weight. 29-32 The DPP-4 inhibitors have a reduced incidence of hypoglycemia compared with sulfonylureas, primarily because of their glucose-dependent effects on insulin secretion. The most common adverse effects of DPP-4 inhibitors are nasopharyngitis, respiratory tract infection, and headache. 30-33

Although DPP-4 inhibitors effectively reduce HbA1c levels, the durability of their glycemic control and their protective effects on β-cell function have not been evaluated in long-term clinical trials. These agents do not appear to increase cardiovascular risk. 34 However, clinical trials are underway to assess the effects of DPP-4 inhibitors on cardiovascular outcomes (eg, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results—A Long Term Evaluation [LEADER]; Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus Trial [SAVOR-TIMI 53]; Sitagliptin Cardiovascular Outcome Study [TECOS]).

**Novel Combinations and Applications**

A common question in the clinical application of incretin-based treatments is, “Can a GLP-1 receptor agonist and a DPP-4 inhibitor be administered in combination?” Although, to my knowledge, there have been no clinical studies evaluating such combinations, it is suspected that the combinations would produce minimal benefits on glycemic control and potentially cause adverse effects.

Recent studies have examined the use of incretins in combination with insulin as treatment for patients with T2DM. 35,36 The rationale for such a combination is that the different therapeutic approaches have complementary effects. Insulin controls FPG and nocturnal glucose levels, while GLP-1 receptor agonists and DPP-4 inhibitors control PPG levels and, to a lesser extent, FPG levels. Insulin tends to increase body weight, whereas incretins typically have neutral or beneficial effects on weight. Accumulating data indicate that concomitant insulin and incretin therapy results in improvements in several measures of glycemic control, compared with that of either therapy alone. 35,37,38 Furthermore, such a combination does not increase rates of hypoglycemia, and the weight-neutral or weight-reduction features of incretins persist despite the use of insulin. 35,37,38

The GLP-1 receptor agonists have also been investigated in patients with type 1 diabetes mellitus. In small, preliminary studies, exenatide and liraglutide resulted in reductions in the HbA1c level, insulin dose, and glucose excursions in such patients. 39,40 In addition, ongoing trials are investigating the combination of GLP-1 receptor agonists and insulin in a single delivery device.

Recognition that GLP-1 plays a role in satiety and food intake led to interest in which may improve gastrointestinal tolerability. 23

Another GLP-1 receptor agonist in clinical development is once-daily, exendin-4-based lixisenatide. 24

**DPP-4 Inhibitors**

Inhibition of the DPP-4 enzyme, which rapidly inactivates GLP-1, provides another approach to increasing GLP-1 levels in patients with T2DM. Dipetidyl peptidase-4 inhibitors increase GLP-1 levels to a peak of 30 pmol/L, compared to the 60 pmol/L peak level attained with GLP-1 receptor agonists. 25 Three oral DPP-4 agents are available in the United States: sitagliptin, saxagliptin, and, most recently, linagliptin. Differences of agent actions within this class can be attributed to variations in metabolism and excretion.

Sitagliptin, the first DPP-4 inhibitor to receive FDA approval, entered the US market in 2006 as an adjunctive treatment to diet and exercise. It is administered as a single daily oral dose and is excreted renally, with approximately 79% of the drug excreted unchanged in individuals with normal renal function. 26 As such, dose adjustments are required in patients with moderate to severe renal impairment.

Subsequent to sitagliptin’s availability, saxagliptin received FDA approval. Saxagliptin is also administered orally once daily and is indicated as an adjunct to diet and exercise. 27 Saxagliptin undergoes hepatic metabolism and is predominantly excreted in the kidneys. Dosage adjustments are required in patients with severe renal insufficiency. 27

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**Table 2. Characteristics of Exenatide and Other Investigational GLP-1 Receptor Agonists**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Structure</th>
<th>Dosing Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exendin-4-Based GLP-1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exendin-4 long-acting release</td>
<td>Peptide incorporated in biodegradable polymeric microspheres</td>
<td>Once weekly</td>
</tr>
<tr>
<td>Lixisenatide</td>
<td>Modified with additional C-terminal lysine residues</td>
<td>Once or twice daily</td>
</tr>
<tr>
<td><strong>Human GLP-1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albiglutide</td>
<td>Genetically fused to human serum albumin; single amino acid substitution to confer dipetidyl peptidase-4 resistance</td>
<td>Once weekly</td>
</tr>
</tbody>
</table>

Abbreviation: GLP-1, glucagon-like peptide-1.
in using GLP-1 receptor agonists in the treatment of obese patients without diabetes mellitus. However, as of late 2011 there were few published data on the use of GLP-1 receptor agonists for the management of obesity. These agents are also being investigated as part of combination therapies with other hormones that regulate appetite.

Conclusion

Incretin-based agents play an increasingly important role in the therapeutic paradigm for patients with T2DM. Incorporating GLP-1 receptor agonists into treatment can improve the physiologic role of GLP-1, which is impaired in patients with T2DM. The beneficial effects of these agents extend beyond glucose control and include weight loss and potential restoration of β-cell function.

References


2. DeFronzo RA. From the triumvirate to the ominous paradigm for patients with T2DM. The beneficial role of GLP-1, which is impaired in patients with T2DM. Incor-
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