

# Incretin-Based Therapies

## A Clinical Need Filled by Unique Metabolic Effects

### Learning Objectives

- List the 2 major pathophysiologic defects associated with type 2 diabetes.
- Discuss the barriers to achieving tight glycemic control in type 2 diabetes.
- Describe the effects of incretin hormones on glucose metabolism.

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**I**n conjunction with the rising prevalence of diabetes, there is an urgent need for strategies that promote tight glucose control, as an overwhelming majority of patients are not meeting glycemic targets. Many current options for intensive diabetes therapy address only one aspect of the underlying pathophysiologic defects associated with type 2 diabetes. The new incretin-based therapies offer unique effects on metabolism, including stimulation of glucose-dependent insulin secretion, suppression of postprandial glucagon secretion, and the promotion of satiety and weight loss. This review will address the pathophysiology of type 2 diabetes and the rationale underlying incretin-based therapies.

### The Diabetes Epidemic

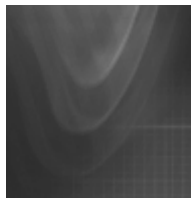
In 2002, nearly 18.2 million people in the United States were believed to have diabetes (~6.3% of the population).<sup>1</sup> Uncontrolled diabetes results in significant morbidity and mortality, including cardiovascular disease, blindness, end-stage renal disease, and amputations.<sup>1</sup> The total cost of diabetes in the United States in 2002 was nearly \$132 billion in medical expenditures

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and lost productivity.<sup>1</sup> It has been predicted that there will be at least 333 million adults in the world with type 2 diabetes by the year 2025.<sup>2</sup> The increasing prevalence of diabetes is driven by an increase in obesity.<sup>3</sup> Most disturbing, both obesity and type 2 diabetes are becoming more common in children and adolescents, placing them at a higher risk for diabetic complications at an earlier age.<sup>4,6</sup>

## Pathophysiology of Type 2 Diabetes

Both genetic factors and environmental factors (eg, obesity) are thought to contribute to the development of type 2 diabetes. Type 2 diabetes is characterized by insulin resistance or a decreased sensitivity to insulin in the liver, muscle, and adipose tissue. As a result of insulin resistance, hyperinsulinemia may occur as the pancreatic  $\beta$  cells produce more insulin in an effort to overcome the insulin resistance. Over time, there is a progressive decline of insulin-producing pancreatic  $\beta$  cells among patients with type 2 diabetes,<sup>7</sup> which ultimately leads to a relative insulin deficiency.

Because insulin was the only available treatment for diabetes for many years, it is often viewed as the principle glucoregulatory hormone. Indeed, insulin plays an important role in glucoregulation. In healthy individuals, it is secreted in response to increased blood glucose levels following nutrient ingestion. Insulin regulates postprandial glucose levels by stimulating glucose uptake and by inhibiting glycogenolysis and gluconeogenesis.<sup>8</sup> Insulin, however, is not the only glucoregulatory hormone. In fact, there are numerous other hormones involved in glucose regulation. Another key player is the  $\alpha$ -cell hormone glucagon. When plasma glucose levels are low, glucagon increases hepatic glucose production. It stimulates both gluconeogenesis and glycogenolysis. During the fed state, however, glucagon is suppressed following nutrient ingestion in healthy individuals. These actions work together to maintain blood glucose levels within a narrow range. The counterregulatory roles of insulin and glucagon are shown in Figure 1.

Although postprandial glucagon secretion is suppressed in healthy individuals, individuals with type 2 diabetes may exhibit a defect in the suppression of glucagon, and postprandial hyperglucagonemia results. This failure to suppress glucagon production postprandi-

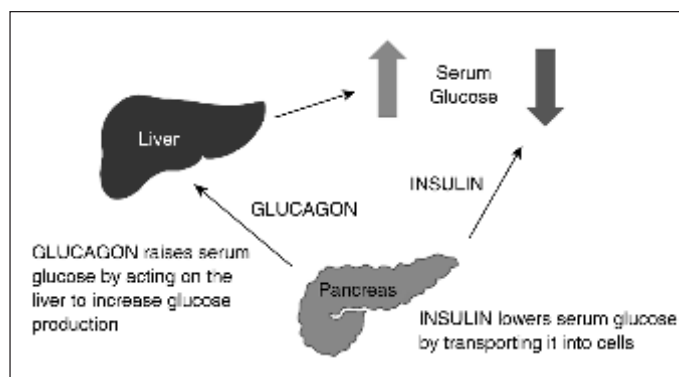


Figure 1. The counterregulatory roles of insulin and glucagon.

ally is associated with an increase in hepatic glucose production. Furthermore, exogenous insulin administration may not completely correct postprandial hyperglucagonemia and, consequently, is less effective at ameliorating the elevated postprandial glucose levels that people with diabetes experience.

In summary, type 2 diabetes is associated with insulin resistance and a progressive decline in  $\beta$ -cell function over time. Although insulin plays an important role in glucoregulation by stimulating glucose uptake and by inhibiting gluconeogenesis and glycogenolysis, other hormones such as glucagon are involved in maintaining glucose homeostasis. Although glucagon is suppressed postprandially in healthy individuals, people with type 2 diabetes fail to do so, further contributing to hyperglycemia in type 2 diabetes. Accordingly, a treatment for type 2 diabetes that addresses not only deficits in insulin secretion but also postprandial hyperglucagonemia would provide a unique therapeutic benefit over other available treatment options.

## The Glycemic Conundrum

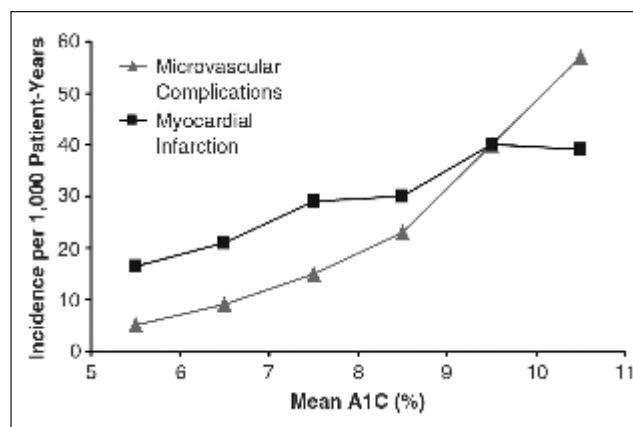
Tight glycemic control is still the best known strategy for reducing mortality and morbidity associated with diabetes. The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that tight glycemic control was associated with a decrease in microvascular complications among patients with type 2 diabetes (Figure 2).<sup>9</sup> Although it has not been demonstrated in a randomized clinical trial, epidemiological evidence has shown that postprandial hyperglycemia is associated with a 2-fold increase in death from myocardial infarc-

tion and stroke.<sup>10,11</sup> Furthermore, many patients who have A1C levels within the target range still may have elevated postprandial hyperglycemia. Accordingly, it becomes increasingly important to manage postprandial glycemia as patients approach glycemic targets (Figure 3).<sup>12</sup> Thus, glycemic control is an important part of reducing morbidity and mortality associated with type 2 diabetes.

Because tight control has been shown to reduce the risk of diabetic complications, a number of organizations have created guidelines for glycemic control. The American Diabetes Association recommends a target A1C <7%, a fasting glucose range of 90 to 130 mg/dL (5.00-7.22 mmol/L), and a postprandial target of <180 mg/dL (10.0 mmol/L).<sup>14</sup> The American College of Endocrinology makes more stringent recommendations, including an A1C <6.5%, a fasting target of <110 mg/dL (6.11 mmol/L), and a postprandial target of <140 mg/dL (7.78 mmol/L).<sup>15</sup> The International Diabetes Federation also recommends a target A1C <6.5%. However, it recommends that fasting glucose levels should be <100 mg/dL (5.56 mmol/L) and postprandial glucose should be <145 mg/dL (8.06 mmol/L).<sup>16</sup> Glycemic targets appear in Table 1.

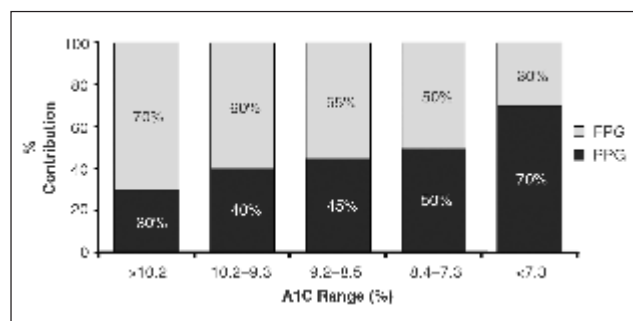
Health care providers are faced with evidence demonstrating that tight glycemic control reduces the risk of diabetic complications coupled with epidemiological data that demonstrated a continued decline in glycemic control in the population of people with diabetes. Although intensive insulin treatment improved glycemic control in the UKPDS, only 28% of insulin-treated patients in the study were able to maintain A1C levels below 7% over a 9-year period.<sup>9</sup> Despite the emphasis on glycemic guidelines and targets, patients with type 2 diabetes are not meeting these recommendations. Recent epidemiologic data demonstrated that only 36% of people with type 2 diabetes meet the American Diabetes Association target of A1C <7%,<sup>17</sup> and even fewer reach an A1C target of <6.5%.<sup>18</sup> Furthermore, glycemic control appears to be on the decline, with more patients meeting targets in the National Health and Nutrition Examination Survey III (NHANES III; 1988-1994) than in NHANES 1999-2000.<sup>17</sup>

Although the newer insulin analogs, insulin delivery devices, and a wealth of available oral agents have improved treatment outcomes for people with diabetes, a strong trade-off still exists between tight glycemic con-



**Figure 2.** The relationship between glycemic control and diabetic complications.

From Stratton et al.<sup>13</sup> Reprinted with permission from the BMJ Publishing Group.



**Figure 3.** The relationship between A1C, fasting plasma glucose, and postprandial plasma glucose.

Reprinted with permission from Monnier et al.<sup>12</sup>

control and side effects such as weight gain and hypoglycemia.<sup>19-21</sup> One-year weight changes associated with the initiation of several different pharmacologic therapies for type 2 diabetes appear in Figure 4.<sup>22</sup> Because of the barriers associated with insulin and oral medications, patients and physicians alike are often resistant to advancing therapy.<sup>23-25</sup> Patients frequently remain on the same therapeutic regimen for more than a year, despite having A1C values higher than 8%.<sup>26</sup> Primary care physicians and endocrinologists are equally likely to fail to advance inadequately controlled patients.<sup>27</sup> Because of the many clinical barriers associated with insulin and oral medications, there is a great need for a therapy with fewer limiting factors so that patients and physicians alike are less reluctant to advance therapy in a timely manner.

## The Incretin Effect

Because of the progressive nature of type 2 diabetes and the clinical challenges associated with achieving optimal glycemic control, an entirely new therapeutic class of pharmacologic agents based on the action of incretin hormones has been developed. Incretin hormones are gastrointestinal hormones that are released following food ingestion. Research has demonstrated that insulin secretion in response to ingested glucose is greater than insulin secretion that occurs when similar amounts of glucose are infused intravenously (Figure 5). This so-called “incretin effect” led to the hypothesis that gastrointestinal factors play an important role in stimulating insulin secretion.<sup>29-31</sup>

Two principle incretin hormones have been identified: glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Both GLP-1 and GIP play a role in the stimulation of insulin secretion and help facilitate glucose homeostasis following nutrient ingestion. Synthesis of GLP-1 occurs in the L cells, which are located primarily in the ileum and colon. GIP is released by intestinal K cells in the duodenum and proximal jejunum.<sup>32</sup> Both GLP-1 and GIP are rapidly inactivated by dipeptidyl peptidase IV (DPP-IV).<sup>32,33</sup>

## Incretin Actions

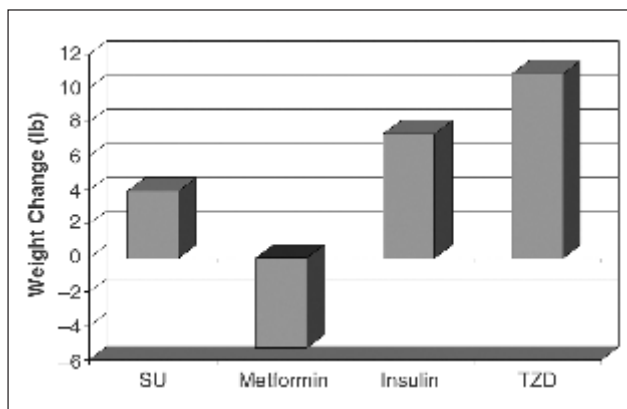
In healthy humans, GLP-1 has been shown to act directly on a variety of different targets to stimulate insulin secretion, suppress glucagon secretion, and delay gastric emptying.<sup>34,35</sup> It has also been shown to promote satiety and reduce food intake and weight.<sup>36</sup> GIP has effects on insulin secretion and gastric emptying but does not affect glucagon secretion, satiety, or weight.<sup>32</sup> A comparison of the effects of GLP-1 and GIP appears in Table 2. In contrast to healthy individuals, people with type 2 diabetes secrete relatively normal amounts of GIP, but its effects are severely impaired in this group.<sup>37</sup> Conversely, people with type 2 diabetes show a reduction in meal-stimulated GLP-1 secretion, although they retain sensitivity to its actions.<sup>38,39</sup> Research has demonstrated that increasing exposure to GLP-1 has beneficial effects for people with type 2 diabetes, including the promotion of glucose-dependent insulin secretion, suppression of postprandial glucagon secretion, promotion of feelings of satiety, and reduction in weight.<sup>40-42</sup> GLP-1 has also been shown to have beneficial effects on  $\beta$ -cell

Table 1

### Glycemic Targets

Glycemic Target	ADA	ACE	IDF
A1C, %	<7.0	≤6.5	<6.5
Fasting glucose, mg/dL	90-130*	<110*	<100†
Postprandial glucose, mg/dL	<180*‡	<140*‡	<145†

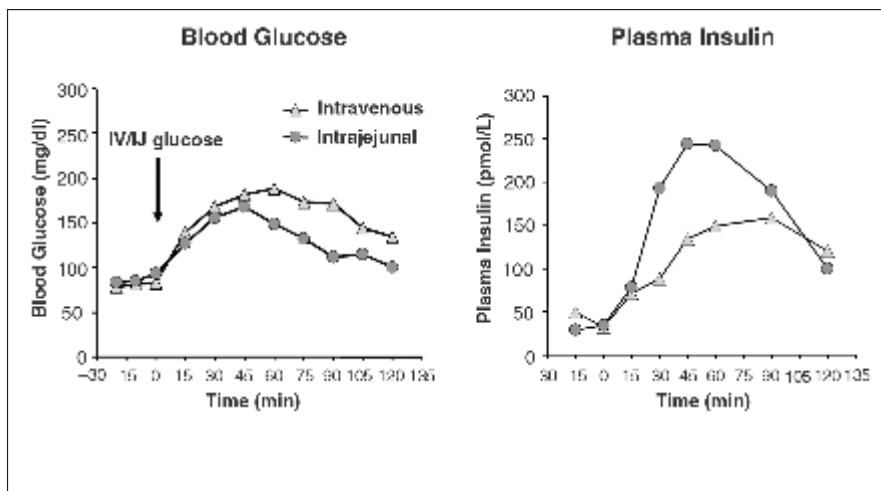
American Diabetes Association (ADA),<sup>14</sup> American College of Endocrinology (ACE),<sup>15</sup> and International Diabetes Federation (IDF) Clinical Guidelines Task Force.<sup>16</sup>  
 \*Plasma equivalent.  
 †Self-monitored blood glucose.  
 ‡Two hours.



**Figure 4.** Weight changes associated with antihyperglycemic therapies. Copyright © 2005 American Diabetes Association. From Diabetes, Vol. 54, Supplement 1, 2005.<sup>28</sup> Reprinted with permission from The American Diabetes Association.

function in animal models and in human islets studied in vitro.<sup>43,44</sup> Because of these differences, therapies that are based on the actions of GLP-1 are more attractive for the treatment of type 2 diabetes.

Because GLP-1 is rapidly inactivated by the enzyme DPP-IV, native GLP-1 would have to be provided via a continuous infusion to produce any therapeutic benefit. Because that approach is not feasible, 2 strategies have been employed to increase exposure to GLP-1 among people with type 2 diabetes. First, GLP-1 receptor agonists that are resistant to the effects of the degrading enzyme DPP-IV are being developed. The first of these compounds, exenatide (BYETTA®;



**Figure 5.** The incretin effect. Reprinted from McIntyre et al<sup>29</sup> with permission from Elsevier.

Table 2

A Comparison of Glucagon-like Peptide 1 (GLP-1) and Glucose-Dependent Insulinotropic Polypeptide (GIP) Action in Type 2 Diabetes

GLP-1	GIP
Stimulates glucose-dependent insulin secretion	Modest effect on glucose-dependent insulin secretion
Inhibits glucagon secretion	No significant inhibition of glucagon secretion
Promotes satiety and reduces body weight	No significant effect on satiety or body weight
Delays gastric emptying	Modest effects on gastric emptying

Adapted from Drucker.<sup>32</sup>

Amylin Pharmaceuticals, Inc, San Diego, Calif), was approved by the US Food and Drug Administration (US FDA) for the treatment of type 2 diabetes among people not adequately controlled by metformin, sulfonylurea (SU), or metformin and SU combination therapy. Liraglutide (Novo Nordisk, Princeton, NJ), a GLP-1 analog that is resistant to DPP-IV, is currently undergoing clinical testing.<sup>45</sup> A second strategy for development of incretin-based therapies is to create compounds that inhibit the action of DPP-IV, thus increasing the activity of GLP-1. These 2 strategies produce agents that differ

on a number of characteristics. GLP-1 receptor agonists such as exenatide are associated with weight loss, whereas DPP-4 inhibitors are weight neutral. DPP-IV inhibitors, however, are not associated with the same dose-dependent nausea seen with GLP-1 receptor agonists. DPP-IV inhibitors are orally available, whereas GLP-1 receptor agonists are delivered via injection.

### Conclusion

The effects of the epidemics of diabetes and obesity are just beginning to emerge. The human and economic toll of these conditions is predicted to increase dramatically over the next 20 years. Among people with diabetes, tight glycemic control is essential for the prevention of diabetic complications, including blindness, amputation, end-stage renal disease, heart attack, and stroke. A substantial number of patients with diabetes fail to meet glycemic targets because of a number of clinical and treatment-related barriers, including side effects, failure of many agents to ameliorate postprandial hyperglycemia, and the progressive nature of type 2 diabetes. Accordingly, there is a strong need for a treatment that can overcome these barriers.

come these barriers.

An entirely new class of medications based on the action of incretin hormones has been developed. The incretin hormones GLP-1 and GIP are secreted in response to nutrient ingestion. Of the 2, GLP-1 has the more desirable properties; it has been shown to work on a variety of different targets to stimulate glucose-dependent insulin secretion, suppress postprandial glucagon secretion, delay gastric emptying, and promote satiety and weight loss. Although people with type 2 diabetes have reduced GLP-1 secretion, they retain sensi-

tivity to its actions, making it an attractive therapeutic target. Because GLP-1 is rapidly degraded by the enzyme DPP-IV, GLP-1 receptor agonists that are resistant to the effects of DPP-IV and compounds that inhibit the effects of DPP-IV are being developed. The first of these compounds, the incretin mimetic exenatide, was approved by the US FDA in April 2005.

## Ask the Expert

**Q:** What is the most appropriate postprandial glycemic target for patients with type 2 diabetes?

**A:** The target for postprandial glucose (PPG) may vary depending on the guidelines one follows; however, most authorities agree that the PPG should not be higher than 135 to 140 mg/dL (7.50-7.78 mmol/L).

**Q:** Why is there no consistency in glycemic targets, with some guidelines recommending A1C <7% and others recommending A1C <6.5%?

**A:** Guidelines that emanate from various agencies or panels reflect numerous points of view, including the facility or difficulty in achieving lower glycemic targets with currently available agents and the risks (hypoglycemia) associated with intensified therapeutic regimens. Most health care practitioners would agree that a normal A1C is an ideal target for an individual patient, if this goal can be achieved safely.

**Q:** Does the number of calories consumed or the micronutrient composition of a meal affect the rise in GLP-1 and GIP seen among healthy people?

**A:** The secretion of incretin hormones is directly proportional to the number of calories consumed. In general, fats are the most potent stimulus, but carbohydrates and protein also stimulate GIP and GLP-1 secretion.

**Q:** Since GLP-1 inhibits glucagon secretion during periods of hyperglycemia, does the liver continue to store adequate amounts of glycogen to respond to lower blood glucose?

**A:** The inhibition of glucagon secretion is glucose dependent. Once glucose returns to normal, glucagon suppression is terminated, and the liver sees higher levels of glucagon as a defense against hypoglycemia.

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