A Physiologic and Pharmacological Basis for Implementation of Incretin Hormones in the Treatment of Type 2 Diabetes Mellitus

JEFFREY S. FREEMAN, DO

Progressive deterioration of β -cell function is a hallmark of type 2 diabetes mellitus (DM). Together with increasing insulin resistance in peripheral tissues (in both the liver and the skeletal muscle), the inability of pancreatic insulin secretion to manage fasting and postprandial glucose levels results in hyperglycemia. Currently available oral antidiabetes agents improve glycemic parameters, but no single drug addresses the numerous pathophysiologic defects known to contribute to hyperglycemia in patients with type 2 DM. Dysregulation in the incretin system is another component of the pathophysiologic processes that lead to DM. Agents used to correct defects in the incretin system, such as glucagon-like peptide 1 receptor agonists and dipeptidyl peptidase 4 inhibitors, offer the potential to restore glucose-dependent insulin secretion and improve β -cell function. Glucagon-like peptide 1 receptor agonists also promote weight loss and provide beneficial effects on cardiovascular risk factors. A new approach that promotes the selection of pharmacotherapy for the treatment of patients with DM, with the goal of slowing or reversing the natural history of the disease, may be in order. Clinicians can select agents to address specific pathophysiologic defects to improve glycemia, with the hope of preventing the development of complications.

Mayo Clin Proc. 2010;85(12)(suppl):S5-S14

ADA = American Diabetes Association; AE = adverse event; CI = confidence interval; DM = diabetes mellitus; DPP-4 = dipeptidyl peptidase 4; EASD = European Association for the Study of Diabetes; GIP = glucose-dependent insulinotropic polypeptide; GLP-1 = glucagon-like peptide 1; HbA_{1c} = hemoglobin A_{1c}; IRAS = Insulin Resistance Atherosclerosis Study; LEAD = Liraglutide Effect and Action in Diabetes; LEADER = Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results—A Long-term Evaluation; TECOS = Trial Evaluating Cardiovascular Outcomes with Sitagliptin; UKPDS = United Kingdom Prospective Diabetes Study

The pathophysiologic defects that characterize type 2 diabetes mellitus (DM) include insulin resistance in liver and skeletal muscle and pancreatic β -cell dysfunction. Initially, β cells are able to increase insulin secretion sufficiently to offset insulin resistance, thus maintaining normoglycemia. When β cells are no longer able to compensate, plasma glucose levels increase.¹ Recent findings indicate that defects in β -cell function and increased insulin resistance occur early in the natural history of type 2 DM and can be present for 3 to 6 years before diagnosis.² Also, DM-related complications or tissue damage is evident in approximately 50% of individuals with type 2 DM at the time of diagnosis.³

Progressive β -cell dysfunction is pathognomonic of the natural history of type 2 DM. Data from the longitudinal United Kingdom Prospective Diabetes Study (UKPDS) 16 showed that, over time, patients experience increasing

hyperglycemia together with decreasing β -cell function, regardless of the therapeutic interventions administered. Even patients receiving intensive therapy that improved mean hemoglobin A_{1c} (HbA_{1c}) levels from 6.9% at baseline to 6.1% at 1 year showed deterioration of results over time; after 6 years, the mean HbA_{1c} level for these patients was 7.1%.⁴ In UKPDS 49, the proportion of patients who maintained target glycemic levels decreased markedly during 9 years of follow-up. This decrease is consistent with progressive deterioration in β -cell function, such that only 50% of patients maintained their glycemic goal with monotherapy at 3 years and only 25% of patients at 9 years.⁵

The Insulin Resistance Atherosclerosis Study (IRAS) showed that continuous decrease in β -cell function, primarily with respect to short-term insulin response, leads to disease progression.⁶ In the evolution of type 2 DM, β -cell function decreases progressively, resulting in diminished glucose tolerance, regardless of the patients' ethnic background.⁷ Early postprandial increments of insulin are delayed and reduced in patients with type 2 DM; this is an early indicator of the development of diabetes.^{8,9}

The main underlying defect in type 2 DM responsible for the deterioration of glycemic control is the progressive decrease in β -cell function that results in inadequate insulin secretion. In addition, excessive secretion of glucagon by pancreatic α cells further contributes to glycemic dysregulation.¹⁰ Glucagon promotes hepatic glucose production and potentiates hepatic glucose mobilization, further exacerbating hyperglycemia.¹¹ Finally, recent studies have defined other pathophysiologic changes associated with the development of type 2 DM, such as defects in the incretin system.

This article reviews our current understanding of the pathogenesis of hyperglycemia and its complications in patients with type 2 DM, with a specific emphasis on the mechanisms by which different therapeutic agents address the inherent pathophysiologic defects of type 2 DM.

From the Division of Endocrinology and Metabolism, Philadelphia College of Osteopathic Medicine, Philadelphia, PA.

Dr Freeman has received speakers' bureau fees from GlaxoSmithKline, Merck & Co, Inc, and Novo Nordisk Inc.

Address correspondence to Jeffrey S. Freeman, DO, 4190 City Ave, Ste 324, Philadelphia, PA 19131-1626 (jeffreymfreemando@aol.com).

© 2010 Mayo Foundation for Medical Education and Research

FIGURE 1. Natural history of type 2 diabetes mellitus. The 3 core pathophysiologic defects likely responsible for the progressive nature of the disease and deterioration in glycemic control, insulin resistance, insulin deficiency, and impaired incretin effect are highlighted, showing their relative function and course. IFG = impaired fasting glucose; IGT = impaired glucose tolerance.

From *Am J Med*,¹² with permission from Elsevier.

EVOLVING CONCEPTS OF DISEASE MECHANISMS IN TYPE 2 DM

The development of type 2 DM is marked by gradual defects in insulin sensitivity (increasing insulin resistance) and insulin secretion by pancreatic β cells, excessive secretion of glucagon by α cells, and impaired incretin effect. Hyperglycemia contributes to vascular changes that lead to DM-related complications. Even before the onset of overt diabetes, the relationship between β -cell function and insulin sensitivity is disrupted (Figure 1).¹² Hyperglycemia results when enhanced insulin secretion is unable to compensate for increasing insulin resistance.¹² However, β -cell function has progressively diminished long before this point. Approximately 80% of β -cell capacity is gone when DM manifests, and up to 50% of patients have already developed complications of type 2 DM at this point.^{1,3}

The natural history and evolution of type 2 DM are complex. Until recently, interactions among the triumvirate of impaired β -cell function leading to diminished insulin secretion, increased hepatic glucose production, and diminished end-organ insulin sensitivity were thought to largely mediate the development of type 2 DM. However, it is now clear that other mechanisms are involved in the develop-

ment of this disease. Hyperglycemia and the emergence of complications are also affected by several factors, including accelerated lipolysis by adipocytes, inappropriately enhanced glucagon secretion by pancreatic α cells, increased renal glucose resorption, insulin resistance in the brain, and incretin deficiency or resistance. Recently, DeFronzo¹ described these complex interactions of pathophysiologic derangements as the “ominous octet” affecting the development of type 2 DM.

The pathogenesis of type 2 DM is summarized in Figure 2.¹³ Insulin resistance and defects in pancreatic β -cell function, which ultimately lead to insufficient insulin, lead to the development of hyperglycemia and subsequent complications.

AGENTS USED TO ADDRESS THE PATHOPHYSIOLOGIC DEFECTS OF TYPE 2 DM

A variety of oral agents are available for treatment of type 2 DM. Drugs of different classes target specific pathophysiologic defects. Therefore, combination therapy may provide advantages for effective glycemic control. Classes of agents with complementary mechanisms of action may be combined for optimal results.¹⁴ The sulfonylureas are insulin secretagogues that lower blood glucose levels by

FIGURE 2. Pathogenesis of type 2 diabetes mellitus. The role of environmental and genetic factors on insulin secretion and insulin resistance. FFAs = free fatty acids; MODY = maturity-onset diabetes of the young. From the American Diabetes Association,¹³ with permission.

stimulating insulin secretion from pancreatic β cells.¹⁴ Metformin is a biguanide that suppresses hepatic glucose production in the presence of insulin. Unlike sulfonylurea therapy, the use of metformin is not associated with hypoglycemia.¹⁴ Thiazolidinediones attenuate insulin resistance by sensitizing the liver and peripheral tissues to insulin and may also preserve β -cell function.^{1,14} Finally, insulin is the most effective hypoglycemic agent in our treatment armamentarium and is recommended by the American Diabetes Association (ADA) as the second agent added after metformin.¹⁵ A recent trial compared metformin plus insulin with triple oral therapy in patients with newly diagnosed type 2 DM. After 3 years, the 2 regimens were equally effective in lowering HbA_{1c} levels and did not cause greater weight gain or hypoglycemia.¹⁶

INCRETIN HORMONES AND THE INCRETIN EFFECT

Incretin hormones, primarily glucagon-like peptide 1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP), are polypeptide hormones synthesized in the gut that stimulate insulin secretion in response to food

consumption. Glucagon-like peptide 1 is secreted from enteroendocrine L cells in the distal aspect of the small bowel and colon in response to neural and/or endocrine factors. GIP is secreted mainly by K cells in the duodenum.¹⁷ The receptor for GIP is expressed on pancreatic β cells and other locations in pancreatic islets. The GLP-1 receptor is predominantly concentrated on β cells, although it is expressed on α and δ cells, as well as in other tissues.¹⁷ The binding of GLP-1 and GIP to their receptors stimulates glucose-dependent insulin secretion through activation of their respective G protein-coupled receptors on pancreatic β cells; ligand binding by the receptors promotes cyclic adenosine monophosphate production and protein kinase A activation.¹⁷ After ingestion of a meal, the incretin hormones GIP and GLP-1 are secreted; they bind to their respective receptors and promote insulin release from β cells.¹⁷ Importantly, incretins exert their effects only when glucose concentrations are above basal levels.¹⁸

As shown in Figure 3,¹⁷ GLP-1 receptors are expressed in tissues other than pancreatic islet cells, including the heart, kidney, central and peripheral nervous systems, liver, and gastrointestinal tract. Because of this, GLP-1 mediates

FIGURE 3. Actions of glucagon-like peptide 1 (GLP-1) in peripheral tissues. The GLP-1 acts directly on the endocrine pancreas, heart, stomach, and brain, whereas actions on liver and muscle are indirect. GI = gastrointestinal.
From *Cell Metab*,¹⁷ with permission from Elsevier.

a variety of diverse glucoregulatory actions. In addition to enhancing glucose-dependent insulin secretion, the binding of GLP-1 to its receptor inhibits glucagon secretion, delays gastric emptying, and suppresses appetite, thereby causing reduced food intake and promoting weight loss. Moreover, GLP-1 facilitates enhanced glucose disposal via neural mechanisms.^{19,20} Together with glucose, GLP-1 stimulates transcription of the insulin gene and stabilizes insulin messenger RNA, thus increasing β -cell insulin stores. In animal models, GLP-1 increases β -cell mass by enhancing proliferation and neogenesis of these cells and inhibiting β -cell apoptosis.²¹ Furthermore, GLP-1 provides cardioprotective and vasodilatory effects. Preclinical research suggests that these actions are mediated via both GLP-1 receptor–dependent and GLP-1 receptor–independent mechanisms.²²

The net result of incretin receptor stimulation is the incretin effect: the increase in insulin is markedly greater in response to an oral than to an intravenous glucose challenge.²³ Indeed, studies have shown that incretin-related stimulation may account for between 50% and 70% of the insulin secreted in response to oral glucose administration.²¹

The incretin effect is diminished in patients with type 2 DM.²⁴ Secretion of GIP is normal or slightly elevated among patients with type 2 DM, but the insulinotropic effects of this hormone are diminished or absent.^{25,26} This

implies that a defect exists at physiologic or even supra-physiologic levels in patients with type 2 DM in response to GIP. In contrast to GIP, diminished secretion of GLP-1 results in reduced levels of this incretin hormone in patients with type 2 DM. Toft-Nielsen et al²⁵ studied 54 patients with type 2 DM, 33 matched controls with normal glucose tolerance, and 15 unmatched individuals with impaired glucose tolerance. The GLP-1 levels were measured during a 4-hour mixed-meal challenge. The area under the concentration time curve from 0 to 240 minutes for GLP-1 (mean $\pm$ SEM) was 3101 ± 198 pmol/L in controls but only 2482 ± 145 pmol/L in patients with type 2 DM ($P = .02$ for type 2 DM vs normal glucose tolerance). The patients with impaired glucose tolerance had a GLP-1 area under the concentration time curve of 2765 ± 185 pmol/L, greater than patients with type 2 DM but less than those with normal glucose tolerance. However, in a separate study, Nauck et al²⁶ investigated the insulinotropic activity of exogenous GLP-1 and GIP in 9 patients with type 2 DM and 9 weight-matched controls. The patients with type 2 DM responded to exogenous GLP-1 with appropriate insulin secretion in a pattern similar to that seen in the controls. In hyperglycemic clamp experiments, controls secreted insulin at 51.4 ± 14.7 nmol/L⁻¹/min in response to GLP-1 infusion, whereas this value was 38.2 ± 18.0 nmol/L⁻¹/min in patients with type 2 DM. The difference was not significant ($P = .14$); in fact,

patients with type 2 DM reached 74% of the increment in insulin secretion in response to GLP-1.

MODULATING THE INCRETIN SYSTEM IN TYPE 2 DM

A better understanding of the incretin system has resulted in the clinical development of a variety of agents for the treatment of DM. The aforementioned observations of the capacity for pancreatic β cells of patients with DM to respond with insulin secretion on administration of exogenous GLP-1 has led to the clinical development of GLP-1 receptor agonists with extended half-lives. Also, the recognition that endogenous GLP-1 is rapidly degraded by dipeptidyl peptidase 4 (DPP-4), a ubiquitous protease, has resulted in the development of DPP-4 inhibitors as another strategy to enhance the glucoregulatory actions of incretin hormones in patients with DM.²⁰ In patients with type 2 DM, therapy with the GLP-1 receptor agonist exenatide resulted in an insulin secretory pattern similar to that seen in healthy individuals for both first- and second-phase insulin responses after an intravenous glucose challenge.²⁷ Similar results were observed with administration of the incretin mimetic liraglutide at 1.25 mg/d in individuals with DM.²⁸ Exenatide lowers HbA_{1c} and both fasting and postprandial plasma glucose levels.^{29,30} Mixed-meal tolerance tests using a double tracer technique helped to elucidate other mechanisms by which GLP-1 receptor agonists attenuate postprandial hyperglycemia. Endogenous glucose production by the liver was suppressed by 45% with exenatide treatment, with increased insulin secretion and diminished glucagon release.³¹ Exenatide administration also resulted in delayed gastric emptying and retention of glucose within the splanchnic area.³¹

Preclinical and clinical studies have sought to evaluate the effects of GLP-1 receptor agonists and DPP-4 inhibitors on β -cell function. Preclinical work has shown that GLP-1 receptor agonists inhibit β -cell apoptosis and stop or slow the progressive destruction of β cells in animals. Experiments in Zucker diabetic rats showed that some of the beneficial effects of GLP-1 receptor agonists on glycemic control may be mediated by increased proliferation of islet cells and pancreatic acinar cells and a diminution in apoptosis. Islet β -cell mass increased 1.6-fold with GLP-1 treatment (islet β -cell mass in saline-infused rats was 7.2 ± 1.5 mg vs 11.6 ± 1.1 mg in GLP-1-treated rats; $P < .01$). The GLP-1 treatment resulted in a 1.4-fold increase in the number of actively dividing β cells and a 3.6-fold decrease in the number of apoptotic β cells ($P < .001$).³² Other studies using freshly isolated human islets showed that GLP-1 receptor agonists inhibit apoptosis and enhance responsiveness to glucose. The GLP-

1-treated islets contained more insulin and demonstrated greater glucose-dependent insulin secretion than control islets not cultured with GLP-1.^{33,34} Experiments in rodents showed that the GLP-1 receptor agonists similarly inhibited β -cell apoptosis.^{35,36} Recent clinical trials have shown a beneficial effect of GLP-1 receptor agonists on β -cell function. In a 20-week study in patients with type 2 DM not adequately controlled with metformin, exenatide improved β -cell function as measured by the disposition index, derived by the hyperglycemic and euglycemic clamp techniques.³⁷ In a 1-year trial, exenatide or insulin glargine was given to patients with type 2 DM not adequately controlled with metformin. Despite similar improvements in HbA_{1c} (-0.8% with exenatide vs -0.7% with insulin glargine), exenatide resulted in significantly greater improvement of β -cell function (a 2.46-fold greater improvement of combined glucose- and arginine-stimulated C-peptide secretion; $P < .001$). Interestingly, after a 4-week off-drug period, β -cell function and glycemic control returned to pretreatment values.²⁹ Improvement in β -cell function, as measured by the homeostasis model assessment of β -cell function and proinsulin-insulin ratio, has been reported with liraglutide in several Liraglutide Effect and Action in Diabetes (LEAD) studies.³⁸

However, results with DPP-4 inhibitors are less definitive. Preclinical studies show increased β -cell mass, and clinical studies demonstrate increased insulin secretion and increased glucose sensitivity of β cells with this class of agents.³⁹ The oral DPP-4 inhibitor sitagliptin produced 2-fold elevations in the levels of GIP and GLP-1 after an oral glucose challenge given 2 hours later. These effects of the drug on the increases in incretin hormone levels were shown to be prolonged because the same results were obtained after a glucose load administered 24 hours after a 200-mg dose of sitagliptin.⁴⁰

In randomized controlled clinical trials, GLP-1 receptor agonists and DPP-4 inhibitors have proven to be safe and efficacious in improving glycemic control in patients with type 2 DM.^{20,41} Although DPP-4 inhibitors improve glycemia, they have no effect on body weight, and their use may be associated with a slight increase in risk of infection.⁴¹ The GLP-1 receptor agonists result in sustained reductions in HbA_{1c} level as well as fasting and postprandial hyperglycemia, and they promote weight loss in most patients.^{30,38} An open-ended, open-label clinical trial that included 217 patients treated with exenatide in addition to metformin and/or sulfonylureas for 3 years showed sustained mean $\pm$ SEM reductions in HbA_{1c} of $-1.1\% \pm 0.1\%$; 46% of patients achieved an HbA_{1c} level of less than 7%. Additionally, weight loss was -1.6 kg at week 12 and continued to progressively decrease to -5.3 kg at 3 years of therapy. A total of 84% of patients lost weight, with 68%

having both a decrease in HbA_{1c} level and body weight. Gastrointestinal adverse events (AEs), including nausea, may occur in up to 30% to 40% of patients; however, the frequency and severity decrease over time in patients who initially experienced nausea.^{30,41,42} In its phase 3 program, liraglutide alone or in combination therapy resulted in reductions of HbA_{1c} levels in the range of -0.6% to -1.5%. In the LEAD-6 trial, which compared liraglutide with exenatide, nausea was reported in approximately 25% of patients in each group.³⁸

In preclinical studies, GLP-1 has been shown to stimulate the C cells of the thyroid, which are the cells of origin of medullary carcinoma of the thyroid and the source of calcitonin.^{43,44} Rats treated with high doses of GLP-1 have developed benign C-cell adenomas.⁴³⁻⁴⁵ However, cases of medullary carcinoma of the thyroid in humans have not been reported.^{42,46} Five cases of papillary thyroid carcinoma have been reported in clinical trials with liraglutide and in one case of an individual treated with a comparator.⁴⁶ Prescribing information for liraglutide has a box warning stating that liraglutide has caused C-cell tumors at clinically relevant exposures in rodents, and it is unknown whether liraglutide causes thyroid C-cell tumors or medullary thyroid cancer in humans.⁴⁶ A recent preclinical study evaluated the effects of native GLP-1 and several GLP-1 receptor agonists (liraglutide, exenatide, tasoglutide, and lixisenatide) on thyroid C cells and their ability to cause calcitonin release and C-cell proliferation.⁴³ All the agents studied activated rodent thyroid C cells, causing calcitonin release in a GLP-1 receptor-dependent manner. Long-term GLP-1 receptor activation was also associated with increased levels of calcitonin messenger RNA, C-cell proliferation, and tumor formation in rats and mice. However, there was no calcitonin release or evidence of C-cell hyperplasia in cyno-molgus monkeys given a GLP-1 receptor agonist dosed at 60-fold the clinical exposure for 20 months, and there was no evidence of calcitonin release after treatment of human C-cell lines. The long-term consequences of sustained GLP-1 receptor activation in the human thyroid remain unknown and merit additional study.⁴³

The incidence of pancreatitis is known to be increased among patients with type 2 DM compared with the general population. A retrospective cohort database analysis included 337,067 patients with type 2 DM, sex and age matched to an equal number of controls who did not have DM. Patients with type 2 DM had a 2.83-fold (95% confidence interval [CI], 2.61-3.06) greater risk of pancreatitis vs those without diabetes.⁴⁷ Pancreatitis has been reported only rarely in patients treated with exenatide, and a claims-based drug safety surveillance system analysis demonstrated no additional risk of developing pancreatitis with either exenatide or sitagliptin treatment.^{48,49} A

recent retrospective cohort study examined the incidence of acute pancreatitis among patients who had recently been treated with exenatide vs other antidiabetes medications. Bloomgren et al⁵⁰ found that current, recent, and past use of exenatide was not associated with an increased rate of acute pancreatitis compared with other antidiabetes agents. In clinical trials, exposure-adjusted incidence rates per 100 patient-years and 95% CIs for pancreatitis were not statistically different between treatment groups (exenatide, 0.28; comparators, 0.26; difference, 0.025 [95% CI, -0.46 to 0.51]).⁵¹ Because there have been post-marketing reports of acute pancreatitis, clinicians should observe patients carefully after initiation of exenatide therapy and after dose increases for signs and symptoms of pancreatitis. If pancreatitis is suspected, exenatide therapy should be discontinued promptly, and appropriate management should be initiated. If pancreatitis is confirmed, exenatide therapy should not be resumed.⁴²

On rare occasions, treatment with liraglutide has been associated with pancreatitis. Eight cases of pancreatitis were reported during intermediate- and long-term trials in the liraglutide clinical development program, 7 of which were in patients treated with liraglutide and 1 in a patient receiving a comparator. Of the 7 cases in liraglutide-treated patients, 5 were reported as acute pancreatitis and 2 as chronic pancreatitis. No conclusive data have established a risk of pancreatitis with liraglutide. After initiation of liraglutide and dose increases, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, the use of liraglutide and other potentially suspect agents should be discontinued. If pancreatitis is confirmed, liraglutide therapy should not be resumed.^{46,52}

In a 2007 systematic review and meta-analysis of the literature on the efficacy and safety of incretin-based therapy, an increased incidence of infection with DPP-4 inhibitors was suggested, particularly nasopharyngitis and urinary tract infection with sitagliptin.⁴¹ However, a recent safety meta-analysis evaluated the general safety and tolerability profile of sitagliptin from more than 10,000 patients with type 2 DM.⁵³ The incidence of infections was no different than with comparators. There were no between-group differences using the terms *nasopharyngitis*, *bronchitis*, and *urinary tract infection*.⁵³

Bruce et al⁵¹ recently reported the results of a meta-analysis to evaluate the safety and tolerability of exenatide and included 11 comparator-controlled clinical trials. Data from 2251 exenatide-treated patients and 1603 comparator-treated patients were reviewed. Mean days of exposure were 172 for the exenatide group and 176 for the comparators. The overall incidence rates for serious AEs were 3.6% and 3.5%, respectively, and the rates of nonserious

AEs were 79% and 64%, respectively. Transient mild-to-moderate nausea, noted in 39.1% of exenatide-treated patients and 8.9% of comparator-treated patients, was the most commonly occurring AE. Vomiting occurred in 13.4% of exenatide-treated patients and in 2.6% of patients receiving comparator therapy. Other AEs ($\geq 5\%$) in the exenatide- and comparator-treated patients included diarrhea (10% vs 4%), nasopharyngitis (8% vs 8%), headache (8% vs 7%), upper respiratory tract infection (7% vs 6%), and dizziness (6% vs 3%). The incidence rates of mild-to-moderate hypoglycemia were similar for exenatide- and comparator-treated patients receiving concomitant sulfonylurea therapy (37% vs 31%). For patients not receiving concomitant sulfonylurea therapy, the incidence rates were 9% and 8%, respectively. Severe hypoglycemia was rare (without a sulfonylurea: exenatide, 0.2%; vs comparator, 0.5%; with a sulfonylurea: exenatide, 0.5%; vs comparator, 0.5%). No statistical differences were evident between the incidences of pancreatitis or renal impairment in the exenatide- and comparator-treated patients. Injection site reactions were noted in 2 patients in clinical trials. In summary, this meta-analysis evaluated more than 1058 patient-years of exenatide exposure and confirmed the overall safety and tolerability of exenatide twice daily.⁵¹

Liraglutide is generally well tolerated. In clinical trials, up to 40% of individuals receiving liraglutide reported nausea, mainly during the first few weeks after initiation of treatment. For most patients, nausea dissipates after several weeks.⁵⁴ The formation of antiliraglutide antibodies has been observed in approximately 10% of patients in clinical trials, but their development does not seem to be associated with deterioration of clinical control.⁵⁴

The GLP-1 receptor agonists may provide benefits other than their actions in improving glycemia. Immediately after angioplasty for acute myocardial infarction, intravenous administration of recombinant GLP-1 ($n=10$) added to background therapy compared with a control solution ($n=11$) significantly improved left ventricular ejection fraction from $29\% \pm 2\%$ to $39\% \pm 2\%$ ($P < .01$) and global and regional myocardial motion score indices from 1.94 ± 0.11 to 1.63 ± 0.9 and 2.53 ± 0.08 to 2.02 ± 0.11 , respectively ($P < .01$ for both). The beneficial effects of GLP-1 were not accounted for by changes in blood pressure or heart rate and were seen in both diabetic and nondiabetic individuals.⁵⁵ Non-glucose-dependent mechanisms may contribute to improved outcomes for cardiac patients. These mechanisms include reductions in nonesterified fatty acid levels, which may be involved in the development of cardiac arrhythmias, and enhancements in endothelial function and microcirculatory integrity. However, the definitive mechanisms remain to be established.⁵⁵

Patients with severe heart failure (New York Heart Association class III/IV; $N=12$), whether they were diabetic or not, experienced improvements in left ventricular ejection fraction (21%-27%; $P < .01$) and functional status (6-minute walk distance, 232-286 m; $P < .001$) with continuous subcutaneous infusion of GLP-1 for 5 weeks. For these patients, cardiac volume and systemic vascular resistance decreased and cardiac output increased, consistent with peripheral unloading.⁵⁶ Additional studies are needed to evaluate the efficacy and safety of GLP-1 receptor agonists for these nonapproved uses.

PATHOPHYSIOLOGY OF TYPE 2 DM: CLINICAL IMPLICATIONS

As our appreciation of the incretin system expands, we can readily envision how agents that affect this system can provide notable clinical benefits to patients with type 2 DM. The GLP-1 receptor agonists not only provide glycemic control but also promote weight loss and improve several parameters related to cardiovascular function. Consequently, patients with DM and elevated cardiovascular risk represent a population that may experience considerable improvements across multiple metabolic issues while receiving treatment with incretin mimetics.¹²

Incretin agents are often used in combination with other antidiabetes medications. Metformin is typically one of the first pharmacological agents offered after diet and exercise have failed to manage type 2 DM. Metformin has been shown to increase GLP-1 levels in obese, nondiabetic individuals after an oral glucose challenge. Investigators speculate that this could be due to the inhibition of GLP-1 degradation by DPP-4.⁵⁷ Additional investigation of this phenomenon in patients with type 2 DM revealed that metformin indeed inhibited DPP-4 activity in fasting individuals. However, when metformin was taken with a meal, the inhibition of DPP-4 was lost, possibly because of lower serum drug concentrations when agents are taken with food.⁵⁸

A new approach for selecting pharmacological agents for the treatment of patients with DM may be warranted. Choosing antidiabetes medications that directly address underlying pathophysiologic defects, with the goal of interrupting or modifying the natural history of the disease, may ultimately enhance outcomes and retard the development of diabetes-related complications. For many patients, a combination of therapies is necessary; judicious selection is imperative.⁵⁷

The ADA and the European Association for the Study of Diabetes (EASD) recently proposed an algorithm for medical management of type 2 DM. The glycemic goal is an HbA_{1c} level less than 7%, and physicians are encouraged

to titrate medications and modify interventions rapidly to achieve glycemic targets. The ADA/EASD guidelines recommend the use of antidiabetes medications with greater and more rapid glucose-lowering properties for individuals whose HbA_{1c} level is greater than 8.5% but acknowledge that patients with recent-onset diabetes or an HbA_{1c} level less than 7.5% may respond adequately to less intensive interventions. Individualized treatment is emphasized.¹⁵

The new American Association of Clinical Endocrinologists/American College of Endocrinology guidelines¹⁴ favor the use of GLP-1 receptor agonists and DPP-4 inhibitors because of their effectiveness and overall safety profiles. With these guidelines, sulfonylureas are a lower priority because of their risk of hypoglycemia and weight gain as well as failure to provide long-term glycemic control. Thiazolidinediones are considered well validated because of their extended durability of action (preserving β -cell function) but have a lower priority because of their AE profile.

The UKPDS 33 showed that, despite the initial improvement in glycemic parameters with intensive therapy, glycemic control was invariably lost, and HbA_{1c} and fasting glucose levels continued to increase progressively over time. The median HbA_{1c} level was 7.09% at baseline for this group. After the first 5 years of the study, the median HbA_{1c} level decreased to 6.6%, but this percentage increased with each successive 5-year period to 7.5% for the second and 8.1% for the third 5-year period.³ With declining β -cell function, suppression of hepatic glucose synthesis by metformin may become less effective.⁵⁹ With insulin secretagogues and metformin, β -cell function diminishes as type 2 DM progresses. Support of β -cell function may have the potential to slow the natural history of type 2 DM.^{59,60}

Treatment with GLP-1 receptor agonists, such as exenatide, produced durable improvements in glycemic parameters. Sustained reductions in HbA_{1c} levels in excess of 1% were sustained for more than 3 years, weight loss was maintained, and β -cell function, as measured by the homeostatic model assessment of β -cell function, was sustained.³⁰ A host of trials are under way and continue to be planned to better understand the effects of antidiabetes medications on preservation of β -cell function.^{29,39,61,62} In addition, the efficacy and safety of the incretin-based agents, although evaluated in relatively short-term clinical studies, await further confirmation from long-term trials.

CONCLUSION

With improved understanding of the underlying mechanisms mediating the development of type 2 DM, clinicians will be better able to select antidiabetes drugs that address

these pathophysiologic defects. Incretin resistance or deficiency contributes to development of hyperglycemia in patients with type 2 DM. Abundant clinical evidence shows that incretin-based therapy corrects these defects and helps improve glycemic control. In patients with type 2 DM, the insulinotropic effect of GLP-1 is maintained. Therapy with GLP-1 receptor agonists enhances both first- and second-phase insulin secretion, leading to reductions in levels of fasting plasma glucose and postprandial glucose and thus HbA_{1c}. The use of GLP-1 receptor agonists in patients with type 2 DM promotes weight loss and provides effective glycemic control. These agents also have shown beneficial effects with regard to cardiovascular risk factors. A number of clinical trials, such as the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) and Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results—A Long-term Evaluation (LEADER), have been initiated to evaluate the role of incretins on cardiovascular outcomes in patients with type 2 DM. Finally, the incretin-based agents, particularly the GLP-1 receptor agonists, have demonstrated beneficial effects in preserving β -cell function in patients with type 2 DM, which addresses a key underlying defect in these patients.

CLINICAL PEARLS

- The natural progression of β -cell decline, not necessarily nonadherence, is at least partially responsible for the need to initiate insulin therapy in individuals who have been taking oral antidiabetes agents for many years.
- A number of different pathophysiologic defects contribute to hyperglycemia in patients with type 2 DM.
- Appropriate management of patients with type 2 DM should address all the pathophysiologic defects associated with the disease and may require combinations of drugs for optimal success.
- The GLP-1 receptor agonists share most of the glucoregulatory functions of native incretin hormones and are resistant to DPP-4 degradation. Administration of these agents leads to glucose lowering, weight loss, and potential beneficial effects on other cardiovascular risk factors.

REFERENCES

1. DeFronzo RA. Banting Lecture: from the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes*. 2009;58(4):773-795.
2. Tabak AG, Jokela M, Akbaraly TN, Brunner EJ, Kivimaki M, Witte DR. Trajectories of glycaemia, insulin sensitivity, and insulin secretion before the diagnosis of type 2 diabetes: an analysis from the Whitehall II study. *Lancet*. 2009;373(9682):2215-2221.
3. United Kingdom Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998;352(9131):837-853.

4. UK Prospective Diabetes Study Group. UK Prospective Diabetes Study 16: overview of 6 years' therapy of type II diabetes: a progressive disease. *Diabetes*. 1995;44(11):1249-1258.
5. Turner RC, Cull CA, Frighi V, Holman RR; UK Prospective Diabetes Study (UKPDS) Group. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). *JAMA*. 1999;281(21):2005-2012.
6. Festa A, Williams K, D'Agostino R Jr, Wagenknecht LE, Haffner SM. The natural course of β -cell function in nondiabetic and diabetic individuals: the Insulin Resistance Atherosclerosis Study. *Diabetes*. 2006;55(4):1114-1120.
7. Kahn SE. The relative contributions of insulin resistance and β -cell dysfunction to the pathophysiology of type 2 diabetes. *Diabetologia*. 2003;46(1):3-19.
8. Bruce DG, Chisholm DJ, Storlien LH, Kraegen EW. Physiological importance of deficiency in early prandial insulin secretion in non-insulin-dependent diabetes. *Diabetes*. 1988;37(6):736-744.
9. Kahn SE, Carr DB, Faulenback MV, Utzschneider KM. An examination of β -cell function measures and their potential use for estimating β -cell mass. *Diabetes Obes Metab*. 2008;10(suppl 4):63-76.
10. Freeman JS. The pathophysiologic role of incretins. *J Am Osteopath Assoc*. 2007;107(suppl 3):S6-S9.
11. Quesada I, Tuduri E, Ripoll C, Nadal A. Physiology of the pancreatic α -cell and glucagon secretion: role in glucose homeostasis and diabetes. *J Endocrinol*. 2008;199(1):5-19.
12. Kendall DM, Cuddihy RM, Bergenstal RM. Clinical application of incretin-based therapy: therapeutic potential, patient selection and clinical use. *Am J Med*. 2009;122(6)(suppl):S37-S50.
13. American Diabetes Association. Pathogenesis. In: Burant CF, ed. *Medical Management of Type 2 Diabetes*. 6th ed. Alexandria, VA: American Diabetes Association; 2008:17-25.
14. Rodbard HW, Jellinger PS, Davidson JA, et al. Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel on type 2 diabetes mellitus: an algorithm for glycemic control. *Endocr Pract*. 2009;15(6):540-559.
15. Nathan DM, Buse JB, Davidson MB, et al; American Diabetes Association; European Association for Study of Diabetes. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2009;32(1):193-203.
16. Lingvay I, Legendre JL, Kaloyanova PF, Zhang S, Adams-Huet B, Raskin P. Insulin-based versus triple oral therapy for newly-diagnosed type 2 diabetes: which is better? *Diabetes Care*. 2009;32:1789-1795.
17. Drucker DJ. The biology of incretin hormones. *Cell Metab*. 2006;3(3):153-165.
18. Kolterman OG, Kim DD, Shen L, et al. Pharmacokinetics, pharmacodynamics, and safety of exenatide in patients with type 2 diabetes mellitus. *Am J Health Syst Pharm*. 2005;62(2):173-181.
19. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet*. 2006;368(9548):1696-1705.
20. Stonehouse A, Okerson T, Kendall D, Maggs D. Emerging incretin-based therapies for type 2 diabetes: incretin mimetics and DPP-4 inhibitors. *Curr Diabetes Rev*. 2008;4(2):101-109.
21. Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. *Gastroenterology*. 2007;132(6):2131-2157.
22. Ban K, Noyan-Asraf H, Hoefler J, Bolz SS, Drucker DJ, Husain M. Cardioprotective and vasodilatory actions of glucagon-like peptide 1 receptor are mediated through both glucagon-like peptide 1 receptor dependent and independent pathways. *Circulation*. 2008;117(18):2340-2350.
23. Elrick H, Stimmler L, Hlad CJ Jr, Arai Y. Plasma insulin response to oral and intravenous glucose administration. *J Clin Endocrinol Metab*. 1964;24:1076-1082.
24. Nauck M, Stöckmann F, Ebert R, Creutzfeldt W. Reduced incretin effect in type 2 (non-insulin-dependent) diabetes. *Diabetologia*. 1986;29(1):46-52.
25. Toft-Nielsen MB, Damholt MB, Madsbad S, et al. Determinants of the impaired secretion of glucagon-like peptide-1 in type 2 diabetic patients. *J Clin Endocrinol Metab*. 2001;86(8):3717-3723.
26. Nauck MA, Heimesaat MM, Orskov C, Holst JJ, Ebert R, Creutzfeldt W. Preserved incretin activity of glucagon-like peptide 1 [7-36 amide] but not of synthetic human gastric inhibitory polypeptide in patients with type-2 diabetes mellitus. *J Clin Invest*. 1993;91(1):301-307.
27. Fehse F, Trautmann M, Holst JJ, et al. Exenatide augments first- and second-phase insulin secretion in response to intravenous glucose in subjects with type 2 diabetes. *J Clin Endocrinol Metab*. 2005;90(11):5991-5997.
28. Vilsbøll T, Brock B, Perrild H, et al. Liraglutide, a once-daily human GLP-1 analogue, improves pancreatic β -cell function and arginine-stimulated insulin secretion during hyperglycaemia in patients with type 2 diabetes mellitus. *Diabet Med*. 2008;25(2):152-156.
29. Bunck MC, Diamant M, Corner A, et al. One-year treatment with exenatide improves β -cell function, compared with insulin glargine, in metformin-treated type 2 diabetic patients: a randomized, controlled trial. *Diabetes Care*. 2009;32(5):762-768.
30. Klonoff DC, Buse JB, Nielsen LL, et al. Exenatide effects on diabetes, obesity, cardiovascular risk factors and hepatic biomarkers in patients with type 2 diabetes treated for at least 3 years. *Curr Med Res Opin*. 2008;24(1):275-286.
31. Cervera A, Wajsborg E, Sriwijitkamol A, et al. Mechanism of action of exenatide to reduce postprandial hyperglycemia in type 2 diabetes. *Am J Physiol Endocrinol Metab*. 2008;294(5):E846-E852.
32. Farilla L, Hui H, Bertolotto C, et al. Glucagon-like peptide-1 promotes islet cell growth and inhibits apoptosis in Zucker diabetic rats. *Endocrinology*. 2002;143(11):4397-4408.
33. Farilla L, Bulotta A, Hirshberg B, et al. Glucagon-like peptide 1 inhibits cell apoptosis and improves glucose responsiveness of freshly isolated human islets. *Endocrinology*. 2003;144(12):5149-5158.
34. Drucker DJ. Glucagon-like peptide-1 and the islet β -cell: augmentation of cell proliferation and inhibition of apoptosis. *Endocrinology*. 2003;144(12):5145-5148.
35. Bregenholt S, Moldrup A, Blume N, et al. The long-acting glucagon-like peptide-1 analogue, liraglutide, inhibits β -cell apoptosis in vitro. *Biochem Biophys Res Commun*. 2005;330(2):577-584.
36. Wang Q, Brubaker PL. Glucagon-like peptide-1 treatment delays the onset of diabetes in 8 week-old db/db mice. *Diabetologia*. 2002;45(9):1263-1273.
37. DeFronzo RA, Triplitt C, Qu Y, Lewis MS, Maggs D, Glass LC. Effects of exenatide plus rosiglitazone on β cell function and insulin sensitivity in subjects with type 2 diabetes on metformin. *Diabetes Care*. 2010;33(5):951-957.
38. Madsbad S. Liraglutide Effect and Action in Diabetes (LEADTM) trial. *Expert Rev Endocrinol Metab*. 2009;4(2):119-129.
39. McGill JB. Impact of incretin therapy on islet dysfunction: an underlying defect in the pathophysiology of type 2 diabetes. *Postgrad Med*. 2009;121(1):46-58.
40. Herman GA, Bergman A, Stevens C, et al. Effect of single oral doses of sitagliptin, a dipeptidyl peptidase-4 inhibitor, on incretin and plasma glucose levels after an oral glucose tolerance test in patients with type 2 diabetes. *J Clin Endocrinol Metab*. 2006;91(11):4612-4619.
41. Amori RE, Lau J, Pittas AG. Efficacy and safety of incretin therapy in type 2 diabetes: systematic review and meta-analysis. *JAMA*. 2007;298(2):194-206.
42. Byetta (exenatide BID) [package insert]. San Diego, CA: Amylin Pharmaceuticals, Inc; 2009.
43. Bjerre Knudsen L, Madsen LW, Andersen S, et al. Glucagon-like peptide-1 receptor agonists activate rodent thyroid C-cells causing calcitonin release and C-cell proliferation. *Endocrinology*. 2010;151(4):1473-1486.
44. Crespel A, DeBoisvilliers F, Gros L, Kervran A. Effects of glucagon and glucagon-like-peptide-1 (7-36) amide on C cells from rat thyroid and medullary thyroid carcinoma CA-77 cell line. *Endocrinology*. 1996;137:3674-3680.
45. Kumar V, Abbas AK, Fausto N, Aster JC. *Robbins and Cotran Pathologic Basis of Disease*. 8th ed. Philadelphia, PA: WB Saunders; 2010.
46. Victoza (liraglutide) [package insert]. Princeton, NJ: Novo Nordisk Inc; 2010. http://www.victoza.com/pdf/Victoza_CombiPI_5.24.pdf. Accessed October 19, 2010.
47. Noel RA, Braun DK, Patterson RE, et al. Increased risk of acute pancreatitis and biliary disease observed in patients with type 2 diabetes: a retrospective, cohort study. *Diabetes Care*. 2009;32(5):834-838.
48. Idris I. FDA reviews incidences of acute pancreatitis in patients taking Byetta. *Diabetes Obes Metab*. 2008;10(1):96-98.

49. Dore DD, Seeger JD, Arnold Chan K. Use of a claims-based active drug safety surveillance system to assess the risk of acute pancreatitis with exenatide or sitagliptin compared to metformin or glyburide. *Curr Med Res Opin.* 2009; 25(4):1019-1027.
50. Bloomgren G, Dore D, Patterson R, Noel R, Braun D, Seeger J. Incidence rates for acute pancreatitis in patients with type 2 diabetes initiating exenatide BID compared to initiating other antidiabetic agents: a retrospective cohort study [abstract 158-OR]. Presented at: American Diabetes Association (ADA) 69th Scientific Sessions; June 5-9, 2009; New Orleans, LA. http://professional.diabetes.org/Abstracts_Display.aspx?TYP=1&CID=74461. Accessed October 19, 2010.
51. Bruce S, MacConell L, Brown C, et al. Safety and tolerability of exenatide BID in patients with type 2 diabetes: integrated analysis of 3854 patients from 11 comparator controlled clinical trials [abstract 578-P]. Presented at: American Diabetes Association (ADA) 69th Scientific Sessions; June 5-9, 2009; New Orleans, LA. http://professional.diabetes.org/Abstracts_Display.aspx?TYP=1&CID=72770. Accessed October 19, 2010.
52. Endocrine and Metabolic Drug Advisory Committee. Liraglutide (injection) for the treatment of patients with type 2 diabetes. NDA 22-341. Briefing document. April 2, 2009. Novo Nordisk, Inc. <http://www.fda.gov/ohrms/dockets/ac/09/briefing/2009-4422b2-02-NovoNordisk.pdf>. Accessed October 28, 2010.
53. Williams-Herman D, Engel SS, Round E, et al. Safety and tolerability of sitagliptin in clinical studies: a pooled analysis of data from 10,246 patients with type 2 diabetes. *BMC Endocr Disord.* 2010;10:7.
54. Deacon CF. Potential of liraglutide in the treatment of patients with type 2 diabetes. *Vasc Health Risk Manag.* 2009;5(1):199-211.
55. Nikolaidis LA, Mankad S, Sokos GG, et al. Effects of glucagon-like peptide-1 in patients with acute myocardial infarction and left ventricular dysfunction after successful reperfusion. *Circulation.* 2004;109(8):962-965.
56. Sokos GG, Nikolaidis LA, Mankad S, Elahi D, Shannon RP. Glucagon-like peptide-1 infusion improves left ventricular ejection fraction and functional status in patients with chronic heart failure. *J Card Fail.* 2006;12(9):694-699.
57. Mannucci E, Ognibene A, Cremasco F, et al. Effect of metformin on glucagon-like peptide-1 (GLP-1) and leptin levels in obese nondiabetic subjects. *Diabetes Care.* 2001;24(3):489-494.
58. Cuthbertson J, Patterson S, O'Harte FP, Bell PM. Investigation of the effect of oral metformin on dipeptidylpeptidase-4 (DPP-4) activity in type 2 diabetes. *Diabet Med.* 2009;26(6):649-654.
59. Nauck MA. Unraveling the science of incretin biology. *Am J Med.* 2009; 122(6)(suppl):S3-S10.
60. Horton ES. Can newer therapies delay the progression of type 2 diabetes mellitus? *Endocr Pract.* 2008;14(5):625-638.
61. DeFronzo RA, Banerji M, Bray GA, et al. Actos Now for the prevention of diabetes (ACT NOW) study. *BMC Endocr Disord.* 2009;9:17.
62. Mari A, Degen K, Brock B, Rungby J, Ferrannini E, Schmitz O. Effects of the long-acting human glucagon-like peptide-1 analog liraglutide on β -cell function in normal living conditions. *Diabetes Care.* 2007;30(8):2032-2033.