

New Therapies for Diabetes

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The role of hormones secreted by the gut in maintaining blood glucose homeostasis has recently been recognized. This recognition has led to the emergence of several novel classes of medications—the glucagon-like peptide-1 (GLP-1) agonists and the dipeptidyl peptidase (DPP)-IV inhibitors—that may target a key element of the underlying pathophysiology of type 2 diabetes mellitus (DM). Both GLP-1 agonists and DPP-IV inhibitors may have the ability to expand β -cell mass. Because the demise of β -cell mass and function is a critical element in the progression of type 2 DM, these agents may have the potential to reverse the natural history of type 2 DM. However, further studies are needed to confirm both long-term β -cell preservation and the role of these agents in the management of diabetes. (*Clinical Cornerstone*. 2007;8[2]:58–65) Copyright © 2007 Excerpta Medica, Inc.

Type 2 diabetes mellitus (DM) has emerged in the past decade as a major global public health dilemma, and the related microvascular and macrovascular complications contribute to the tremendous morbidity and mortality associated with this disease. Ample evidence exists to support a role for meticulous glycemic control in preventing the onset or retarding the progression of complications.^{1,2} Until recently, the major classes of medications available for the treatment of type 2 DM consisted of insulin secretagogues, which stimulate the β -cell to release insulin, and insulin sensitizers, which augment insulin action in the liver and the periphery. However, the natural history of type 2 DM is ultimate β -cell failure, resulting in limited efficacy of these agents over time and ultimately necessitating treatment with insulin.² All too often, at the time that insulin is introduced, the patient has experienced prolonged suboptimal glycemic control with its attendant complications.³

Recent studies have focused on β -cell dysfunction as a pivotal event in the development of hyperglycemia. Impaired insulin secretion has been recognized as the key distinction between insulin-resistant individuals who progress to impaired glucose tolerance and type 2 DM and those who maintain normoglycemia.⁴ The dysregulation of both α - and β -cell dysfunction has also been observed to occur early in the development of type 2 DM, with excessive glucagon release from α -cells occurring concomitantly with reductions in basal insulin secretion.⁵ The new *incretin mimetic* class of agents targets

both aspects of this pathophysiology by enhancing β -cell mass and inhibiting glucagon release (**Table**).

Both glucagon-like peptide-1 (GLP-1) and dipeptidyl peptidase (DPP)-IV inhibitors offer the potential of expanding β -cell mass. Because the demise of β -cell mass and function is a critical element in the progression of type 2 DM, these agents may have the potential to reverse the natural history of this disease. Presently, however, these benefits are largely theoretical in the absence of long-term data confirming β -cell preservation. Ultimately, further studies are needed to fully define the role of these agents in the management of diabetes.

KEY POINT

The natural history of type 2 DM leads to β -cell failure. The new GLP-1 agonists and DPP-IV inhibitors may have the ability to expand β -cell mass and, therefore, may have the potential to reverse the natural history of this disease.

THE ROLE OF GUT HORMONES

The role of gut hormones in maintaining blood glucose homeostasis first became apparent in the 1960s after observations that oral glucose administration stimulates a

TABLE. NOVEL MEDICATIONS FOR THE TREATMENT OF DIABETES.

Class	Drug(s)	Mechanism(s)	Reduction in A1C	Effect on Weight	Administration	Side Effect(s)
GLP-1 Agonist (incretin mimetic)	Exenatide, Liraglutide	Mimics native GLP-1; potentiates insulin secretion; suppresses glucagon; slows gastric emptying; increases β -cell mass	~1%	↓	Subcutaneous	Gastrointestinal
DPP-IV Inhibitor (incretin enhancer)	Sitagliptin, Vildagliptin	Inhibits GLP-1 degradation	0.4%–0.8%	↔	Oral	Possible effects on immune system
Amylin mimetic (synthetic amylin)	Pramlintide	Potentiates insulin action; suppresses glucagon; slows gastric emptying	0.3%–0.6%	↓	Subcutaneous	Gastrointestinal; hypoglycemia

A1C = glycosylated hemoglobin; GLP-1 = glucagon-like peptide-1; DPP-IV = dipeptidyl peptidase-IV.

greater increase in plasma insulin levels compared with an identical amount of insulin administered intravenously.⁶ This phenomenon was termed the *incretin effect* and is believed to account for ~50% to 70% of the total insulin secreted after oral glucose administration.⁶ Subsequent to the incretin effect, 2 major incretin hormones were identified. The first, glucose-dependent insulinotropic polypeptide (GIP), is released from K cells of the jejunum and ileum. The second, GLP-1, is released from intestinal L cells in the distal ileum and colon. Both GIP and GLP-1 are released in response to nutrient ingestion and enhance glucose-stimulated insulin secretion.

NORMAL PHYSIOLOGY

In nondiabetic individuals, glucose homeostasis is generally maintained through a coordinated secretion of insulin and glucagon. Following ingestion of a meal, insulin is released from β -cells in response to rising plasma glucose concentrations, enabling uptake of glucose into the periphery, while glucagon release from α -cells is suppressed. During periods of fasting, including overnight, glucagon secretion predominates, allowing for glycogen breakdown and hepatic gluconeogenesis. In type 2 DM, however, this coordinated interplay is disturbed. Early defects in type 2 DM include delays in insulin secretion and higher postprandial glucagon levels. Overnight insulin levels become inappropriately low and glucagon levels become excessively high.⁷ The islet cells of individuals with type 2 DM also reveal reduced β -cell mass and an increased proportion of α - to β -cells.⁸

THE ROLE OF NATIVE GLP-1

The incretin hormones, particularly GLP-1, have important effects relevant to the pathophysiology of type 2 DM. Native GLP-1 potentiates insulin secretion, particularly in the setting of hyperglycemia, and it is a potent inhibitor of glucagon secretion. As such, it has the potential to restore an altered balance between insulin and glucagon secretion. GLP-1 also stimulates β -cell proliferation and reduces apoptosis. Infusion of GLP-1 has been shown to enhance β -cell mass in animal models.⁹

The limiting factor in clinical use of GLP-1 is its very short half-life of 1 to 2 minutes. Therefore, GLP-1 analogues were developed that are both more potent than native GLP-1 and more resistant to degradation, thus allowing for intermittent rather than continuous infusion. The only currently available GLP-1 analogue, exenatide (previously known as exendin-4), is a GLP-1 receptor agonist that was initially isolated from the venom of the Gila monster (*Heloderma suspectum*). Exenatide was approved by the US Food and Drug Administration (FDA) in 2005. A second GLP-1 agonist, liraglutide, is presently in late-stage clinical development.

THE GLP-1 ANALOGUES: EXENATIDE AND LIRAGLUTIDE

Exenatide

Exenatide is a twice-daily subcutaneously administered medication approved for the treatment of type 2 DM in conjunction with sulfonylureas, metformin, and thiazolidinediones (TZDs). Exenatide is usually administered at a starting dose of 5 μ g and is titrated to a max-

KEY POINT

Native GLP-1 potentiates insulin secretion and is a potent inhibitor of glucagon secretion. As such, it has the potential to restore an altered balance between insulin and glucagon secretion. The GLP-1 analogues are more potent than native GLP-1 and more resistant to degradation.

imum dose of 10 µg twice daily. It is not indicated for use in type 1 DM.

Studies of exenatide have revealed consistent benefits in reducing fasting and postprandial blood glucose levels, glycosylated hemoglobin (A1C) levels, and body weight. Exenatide has been studied in several Phase III trials comparing the addition of exenatide to existing metformin monotherapy,¹⁰ existing sulfonylurea monotherapy,¹¹ and sulfonylurea/metformin combination therapy.¹² Additionally, in a 2007 study,¹³ exenatide treatment was compared with placebo in patients receiving a TZD. In all of these studies, which were 16 to 30 weeks in duration, exenatide reduced A1C levels by ~1% and enabled a greater percentage of patients to achieve a target A1C level <7%. Exenatide also reduced both fasting and postprandial blood glucose levels and was associated with significant weight loss. In a 2007 meta-analysis,¹⁴ which included 7 randomized controlled trials, exenatide was associated with a reduction in fasting blood glucose of 27 mg/dL and a weight loss of 1.44 kg compared with placebo.

Exenatide was also compared with insulin in 2 separate trials: a 26-week trial with glargine¹⁵ and a 52-week trial with biphasic insulin aspart.¹⁶ In both trials, there was a comparable reduction in A1C levels between exenatide and the insulin formulation. Exenatide was associated with superior postprandial blood glucose control in both studies, although treatment with glargine, but not with biphasic insulin aspart, resulted in lower fasting glucose levels compared with exenatide.

Exenatide is consistently associated with gastrointestinal (GI) side effects, primarily nausea, and to a lesser extent, vomiting and diarrhea. The recent meta-analysis¹⁴ found the incidence of nausea to be as high as 57%. The

nausea was generally mild to moderate and was maximal in the initial 8 weeks of use, after which time it attenuated. In nearly all studies of exenatide to date, GI side effects have led to a higher rate of withdrawal than the comparator placebo groups.¹⁴

Monotherapy with exenatide is generally associated with a low rate of hypoglycemia, likely due to its glucose-dependent mechanism of insulin augmentation. Whereas the meta-analysis showed that hypoglycemia was more commonly reported with exenatide than with placebo (16% vs 7%), this effect was predominantly observed with concomitant use of a sulfonylurea.¹⁴

KEY POINT

Exenatide reduces fasting and postprandial blood glucose levels, A1C levels, and body weight, and it is generally associated with a low rate of hypoglycemia. However, it is consistently associated with GI side effects, primarily nausea.

Liraglutide

A second GLP-1 analogue, liraglutide, which is currently in clinical development, will be available as a once-daily subcutaneous therapy. In a recent 14-week study¹⁷ of 5 doses of liraglutide administered as monotherapy, the highest dose of the drug (1.90 mg) was associated with a 1.74% reduction in A1C from a mean baseline of 8.5%, a 2.99-kg reduction in body weight, reductions in fasting glucose and glucagon levels, and improvements in insulin resistance. The side effect profile was notable primarily for GI effects, which decreased over time. No significant hypoglycemia was reported. Although liraglutide and exenatide have not been compared head-to-head, liraglutide has been found less often to be associated with hypoglycemia, but weight loss has also been found to be less pronounced.¹⁴

DPP-IV INHIBITORS

The major enzyme that degrades the native incretin hormones GIP and GLP-1 is DPP-IV. The orally administered *incretin enhancer* class of medications includes the

inhibitors of the DPP-IV enzyme; the DPP-IV inhibitors augment the action of native incretin hormones. Presently, only one DPP-IV inhibitor, sitagliptin, is approved by the FDA. A second DPP-IV inhibitor, vildagliptin, is currently under FDA review, while 2 others are in clinical development.

Initial animal studies suggested a therapeutic role for DPP-IV inhibition. In one study,⁹ DPP-IV–knockout rodents were found to exhibit reduced glycemic excursions after glucose loading in association with increased circulating levels of GLP-1 and insulin. They also exhibited improvements in glycemic control, insulin secretory responses, and hepatic and peripheral insulin sensitivity.

DPP-IV inhibitors have a relatively modest effect on A1C reduction. In Phase II clinical studies,⁷ sitagliptin and vildagliptin were associated with reductions in A1C of 0.4% to 0.6%, with higher A1C reductions observed in patients with higher baseline A1C values. In Phase III studies, 100-mg sitagliptin monotherapy was associated with ~0.8% reduction in A1C and a more substantial 1.52% reduction in patients with baseline A1C levels <9%.¹⁸ Sitagliptin in combination with metformin and pioglitazone has been found to reduce A1C levels by 0.65% and 0.7%, respectively, compared with placebo.^{19,20}

The side effect profile of the DPP-IV inhibitors is favorable, with minimal GI effects and low rates of hypoglycemia. These agents tend to be weight neutral, and they have a favorable weight profile compared with gliptin and TZDs.¹⁴

KEY POINT

The DPP-IV inhibitors have a relatively modest effect on A1C reduction. Their side effect profile is favorable, with minimal GI effects. They exhibit low rates of hypoglycemia, and they tend to be weight neutral.

When data were combined from multiple trials,¹⁴ DPP-IV inhibitors were associated with a number of non-GI effects, including a 1.2-fold increased risk of nasopharyngitis, a 1.5-fold increased risk of urinary tract infections, and a 1.4-fold increased risk of headache. The

increased risk of infection may be related to the ubiquitous nature of the DPP-IV enzyme, which is expressed in many tissues, including lymphocytes.

Sitagliptin is generally administered as a once-daily 100-mg dose. Because the drug is >90% dependent on renal excretion, patients with renal insufficiency and end-stage renal disease require dose reductions to 50 mg and 25 mg, respectively. Vildagliptin has not been shown to accumulate in the setting of hepatic or renal insufficiency; therefore, there does not appear to be a need for dose reductions in these situations with vildagliptin.⁷

PRAMLINTIDE

Pramlintide, an injectable synthetic variant of the hormone amylin, is similar to the incretin mimetic class of medications in that it is a gut hormone that potentiates insulin action. Amylin is a pancreatic hormone that is located within the β -cell and is cosecreted with insulin. Amylin complements the role of insulin in regulating glucose disappearance through a number of mechanisms, including delaying gastric emptying, suppressing postprandial glucagon secretion, and regulating food intake. Amylin has been found to be nearly absent in patients with type 1 DM and deficient in patients with type 2 DM.²¹

Pramlintide received FDA approval in March 2005 for use in both type 1 and type 2 DM as an adjunct to insulin therapy. It is delivered as a mealtime SC injection. In patients with type 1 DM, the starting dose is 15 μ g administered prior to meals, with a target dose of 60 μ g. The doses are more substantial in type 2 DM, with a starting dose of 60 μ g titrated to a target dose of 120 μ g.²¹

KEY POINT

Pramlintide can be used in both type 1 and type 2 diabetes as an adjunct to insulin therapy for the control of postprandial glycemia. However, it requires gradual dose escalation and reduction of the mealtime insulin dose.

The main clinical utility of pramlintide is in the control of postprandial hyperglycemia. Postprandial blood glucose elevations contribute substantially to overall

hyperglycemia as measured by A1C levels, with the relative contribution increasing at lower A1C levels.²² As such, pramlintide offers the potential for improving A1C levels in individuals who are nearly at their A1C goal but who have persistent postprandial hyperglycemia despite optimal use of mealtime insulin analogues. The actual reductions in A1C with pramlintide are modest, however. In clinical trials, 52 weeks of treatment with pramlintide reduced A1C levels by ~0.6% in patients with type 2 DM²³ and ~0.3% in patients with type 1 DM.²⁴

Similar to exenatide, an advantage to pramlintide therapy is its favorable effect on weight. In recent randomized trials, use of pramlintide was associated with a weight loss of 1.1 to 1.4 kg over 6 to 12 months.²⁵ Side effects, like those of exenatide, are primarily GI related, particularly nausea and vomiting. However, its effect on weight appears to be independent of the GI side effects.²⁵

In initial clinical trials of pramlintide with insulin, there was a marked increase in the rate of severe hypoglycemia, especially in individuals with type 1 DM. Therefore, in a subsequent open-label study of pramlintide and insulin, patients were instructed to proactively reduce their mealtime insulin dose by 30% to 50% with initiation of pramlintide. This measure, together with progressive dose escalation of pramlintide, reduced the rate of hypoglycemia in pramlintide-treated patients to rates comparable to those in patients treated with insulin alone.²⁵

Because of the association between pramlintide and insulin-induced hypoglycemia, careful patient selection for pramlintide use is important. Patients should be compliant and on a reasonable glycemic regimen with no significant history of hypoglycemia or hypoglycemic unawareness. Patients should be counseled regarding gradual pramlintide dose escalation and the need to proactively reduce their mealtime insulin dose by 50%. Gastroparesis or use of medications that slow gastric emptying are contraindications to the use of pramlintide. Pramlintide injections should be given prior to meals at sites that are distinct from insulin injection sites. Pramlintide cannot be mixed with insulin.²⁵

CONCLUSIONS

The recent recognition that hormones secreted by the gut play a role in maintaining blood glucose homeostasis has led to the emergence of several novel classes of medications. These medications, in particular GLP-1 agonists and pramlintide, offer the advantages of improvements in

glycemic control without the weight gain that is characteristic of most other drugs in the glycemic armamentarium. The use of these medications may be limited, however, by the necessity of subcutaneous administration and by a GI side effect profile that may be unacceptable to many individuals. DPP-IV inhibitors offer the advantage of being orally administered with an exceedingly favorable side effect profile and a neutral effect on weight. However, they are relatively weak antihyperglycemic agents, and they may increase the risk of some infections. GLP-1 agonists and DPP-IV inhibitors have the potential to reverse the natural history of type 2 DM; however, these benefits are largely theoretical in the absence of long-term data confirming β -cell preservation. Ultimately, further studies are needed to fully define the role of these agents in the management of diabetes.

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Dialogue Box

EDITORIAL BOARD

Why is exenatide contraindicated in type 1 diabetes mellitus (DM)?

GREEN

Exenatide is not approved by the US Food and Drug Administration for use in type 1 DM due, in part, to the paucity of studies in individuals with type 1 DM. There is some evidence that exenatide may augment insulin secretion in type 1 individuals who have recently received an islet cell transplantation. There is also some evidence of a reduction in postprandial hyperglycemia in type 1 individuals treated with exenatide. At this time, however, the use of exenatide in type 1 DM requires further study.

EDITORIAL BOARD

Can exenatide be used in type 2 DM in combined therapy with insulin?

GREEN

Exenatide is not approved in combination with insulin and there are no published data on use of the two together. However, the combination appears to be a rational one in that exenatide augments insulin action and counteracts the opposing effect of glucagon. When I administer the two together to patients on basal-bolus insulin therapy, I generally reduce the prandial insulin by half. If patients are on basal insulin only, I reduce the basal insulin unless the patient's glycemic control is markedly suboptimal.

EDITORIAL BOARD

From a pathophysiologic perspective, wouldn't it be rational to consider an incretin mimetic, such as sitagliptin, as a second-line agent for type 2 DM, to be used after insulin sensitizers and before secretagogues?

GREEN

It is rational from a pathophysiologic standpoint, especially if the goal is β -cell preservation. From a practical perspective, however, one can generally expect a more substantial reduction in glycosylated hemoglobin (A1C)

from a secretagogue than from a dipeptidyl-peptidase (DPP)-IV inhibitor. In addition, DPP-IV inhibitors are costly and lack the long-term safety and efficacy data of many of the secretagogues.

EDITORIAL BOARD

Is there any direct evidence that glucagon-like peptide-1 (GLP-1) agonists or DPP-IV inhibitors enhance β -cell mass?

GREEN

While there is a theoretical basis for these agents enhancing β -cell mass, the evidence is quite limited. There are some animal data revealing a trophic effect of these agents on β -cells. However, a small study in individuals with type 1 DM who received exenatide after islet cell transplantation did not find any evidence of this trophic effect. Further study is needed to answer this vital question.

EDITORIAL BOARD

Do you routinely reduce the dose of a sulfonylurea when you add a GLP-1 agonist or a DPP-IV inhibitor? If so, explain how you accomplish this. If not routinely done, discuss the scenarios where a reduction in dose would be recommended.

GREEN

This decision is highly dependent on patient clinical characteristics, specifically, their baseline glycemic control. In patients with reasonably good glycemic control, I will reduce the dose of a sulfonylurea by ~50% when I add a GLP-1. If I am adding a GLP-1 to improve poor glycemic control, I do not modify sulfonylurea dosing. I often do not reduce the sulfonylurea dose when I add a DPP-IV inhibitor, largely because of the weaker anti-hyperglycemic effect of the DPP-IV inhibitor.

EDITORIAL BOARD

Do you routinely reduce a patient's insulin dosage when you add either a GLP-1 agonist or a DPP-IV inhibitor? Please explain why or why not and, if so, how.

Dialogue Box

GREEN

Again, this is highly dependent on the clinical situation. As with a sulfonylurea, I typically reduce by half bolus insulin (in patients on basal-bolus insulin) or basal insulin (in patients on basal insulin only) when I add a GLP-1 agonist, if the patient has reasonable glycemic control. But I often will need to slowly titrate up again after this initial insulin decrease. In uncontrolled patients, I typically do not modify insulin dosing substantially. Again, because of the weak hypoglycemic effects of DPP-IV inhibitors, I typically do not adjust insulin dosing when initiating DPP-IV therapy.

EDITORIAL BOARD

Can we expect to see DPP-IV inhibitors that have a greater impact on glycemic control any time soon?

GREEN

The second DPP-IV inhibitor, which is presently in late-stage clinical development, has similar A1C reductions to sitagliptin.

EDITORIAL BOARD

How serious an issue is the risk of infection with DPP-IV inhibitors? What precautions would you recommend?

GREEN

This requires further study. Although there is an increased relative risk of infections, the increased absolute risk for nasopharyngitis was 0.3% (6.4 vs 6.1%), and for urinary tract infections (UTIs) it was 0.8% (3.2% vs 2.4%). This yields a number needed to harm of 333 and 125, respectively. These absolute risk increases are relatively modest. In view of the fact that DPP-IV inhibitors are weak hypoglycemic agents, however, it may be reasonable to consider use of an alternative antidiabetic agent in individuals who are prone to nasopharyngitis or recurrent UTIs.