

New Technologies and Therapies in the Management of Diabetes

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Although lifestyle measures are the cornerstone of diabetes therapy, most patients will also require pharmacotherapy to achieve target glucose concentrations. Different classes of antidiabetic agents affect glucose homeostasis through distinct mechanisms (**Figure 1**).¹ Sulfonylureas and the nonsulfonylurea secretagogues (meglitinides) increase endogenous insulin secretion; alpha-glucosidase inhibitors delay intestinal carbohydrate absorption; thiazolidinediones (TZDs) enhance insulin sensitivity primarily by increasing peripheral glucose disposal, but also suppress hepatic glucose production; and metformin, a biguanide, decreases hepatic glucose production, but also increases peripheral glucose disposal to some extent.¹

Despite the number of conventional agents at our disposal, many patients are unable to attain or maintain glycemic goals. The United Kingdom Prospective Diabetes Study of glycemic control with insulin, sulfonylurea, or metformin monotherapy found that approximately 50% of patients were unable to maintain glycemic goals (glycosylated hemoglobin [A1C] <7%) by 3 years, and 75% did not maintain glycemic control by 9 years.² A retrospective study of a health maintenance organization database reported that 26% of patients treated with insulin plus an oral agent and 13% to 30% of those receiving combination therapy with oral agents achieved optimal glycemic control (A1C <7%).³

Although conventional therapy should allow for much better results, unmet needs exist with these therapies. Some of these needs can be addressed with newer agents with different mechanisms of action. Several novel antidiabetic agents have recently become available or are likely to be approved within the next several months. The challenge is to integrate these agents appropriately into the treatment paradigm in ways that will make the best use of their unique attributes.

Insulin

Two new options in insulin therapy have recently become available. Insulin detemir (Levemir), a long-lasting basal insulin, was approved by the US Food and Drug Administration (FDA) in 2005, and an inhaled form of insulin (Exubera) was approved in early 2006.

Abstract

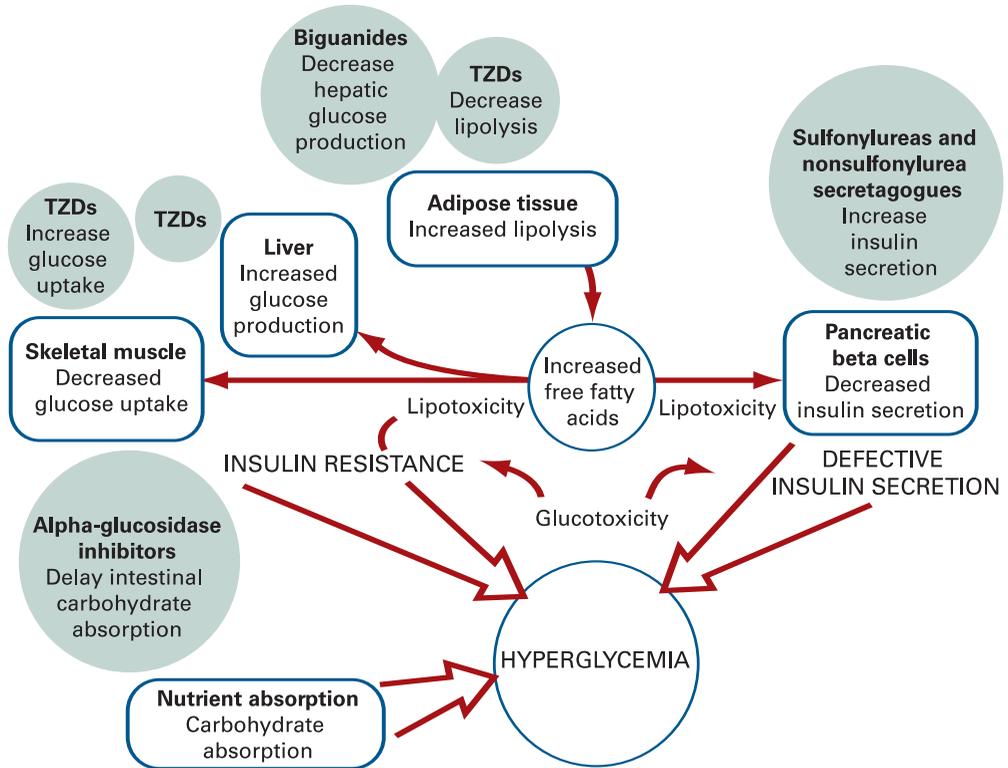
Although there are numerous effective pharmacotherapeutic agents available to treat type 2 diabetes, 5% to 10% of the population with diabetes experience secondary failure. To help combat this issue, it is imperative that clinicians understand the limitations of some current therapies. Secondary failure can be due to decreasing beta cell function, poor adherence to treatment, weight gain, reduction of exercise, changes in diet, or illness.

Glycemic control and cardiovascular risk reduction are of paramount concern; however, the nonglycemic effects of several new therapies to treat diabetes may be advantageous and positively affect the long-term cost of therapy. The discoveries of amylin and glucagon-like peptide-1 have furthered our understanding of the abnormalities involved in diabetes, enabling the development of additional therapeutic options. Incretin-based therapy, including incretin mimetics such as exenatide and the yet-to-be-approved dipeptidyl peptidase-4 inhibitors, and new basal and inhaled insulin may change the way we currently treat type 2 diabetes.

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■ **Figure 1.** Pathophysiological Basis of Conventional Diabetes Therapies



Adapted with permission from Reference 1. TZDs indicates thiazolidinediones.

Figure 2 shows the pharmacokinetics of these new analogs in comparison with other forms of insulin.^{4,6}

Insulin Detemir. Insulin detemir has a unique structure that results in a prolonged duration of action for up to 24 hours. The insulin molecule is acylated with a 14-carbon fatty acid, which allows it to bind reversibly to albumin at the injection site and in plasma. Albumin binding, together with self-association of the molecules at the site of subcutaneous (SC) injection, is responsible for the protracted action of insulin detemir.⁴ A very small percent of albumin molecules are actually bound, however, and there are no known drug–drug interactions between insulin detemir and other drugs that bind albumin.^{4,7}

The pharmacokinetics of insulin detemir are dose-dependent, with lower doses resulting in a shorter duration of action (Table).⁸ In clinical studies, the average daily insulin detemir dose was 0.38 U/kg for adults with type 1 diabetes and 0.77 U/kg for adults with type 2 diabetes.⁷ At these doses,

activity is maintained for approximately 20 to 24 hours, peaking at 8 to 9 hours after administration.⁸ Insulin detemir is typically given once- or twice-daily by SC injection.⁷

Studies have reported that insulin detemir has less within-subject variability and a lower risk of hypoglycemia, particularly nocturnal hypoglycemia, than human neutral protamine Hagedorn insulin.⁹ Treatment with insulin detemir also resulted in lower within-subject variability than insulin glargine.^{10,11}

Inhaled Insulin. The first inhaled form of insulin to be approved by the FDA is Exubera, an insulin inhalation powder. Exubera consists of blisters containing human insulin inhalation powder, which is administered using the Exubera inhaler.¹² The 1-mg and 3-mg doses are approximately equivalent to 3 IU and 8 IU of SC regular human insulin, respectively.

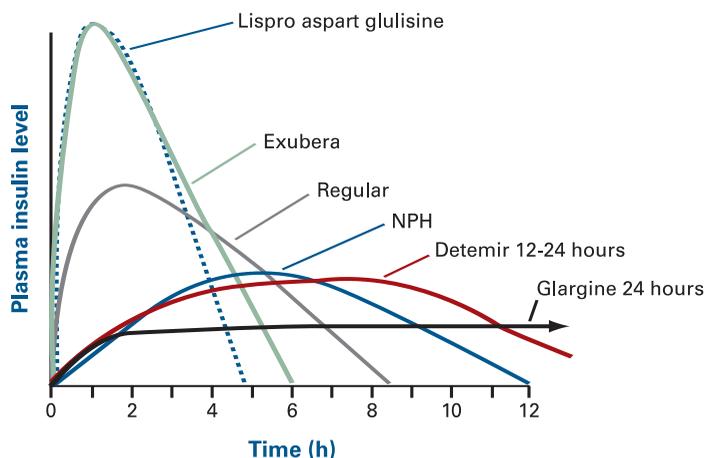
Randomized studies have shown that the efficacy of inhaled insulin is comparable with subcutaneously

injected prandial human insulin in patients with type 1 and type 2 diabetes.^{13,14} In patients with type 2 diabetes, inhaled insulin therapy was associated with improved glycemic control compared with rosiglitazone in patients whose diabetes was not controlled by diet and exercise.¹⁵ Another study evaluated the switch to or addition of inhaled insulin in subjects not at goal despite oral combination therapy.¹⁶ Inhaled insulin, alone or in combination with oral therapy, resulted in significant reductions in A1C compared with continuing combination oral therapy alone (mean adjusted reductions of 1.4% and 1.7%, respectively). A1C levels <7% were achieved by 32% of patients in the inhaled insulin plus oral therapy group, 17% of patients in the inhaled insulin monotherapy group, and 1% of patients who remained on oral combination therapy.¹⁶

Patient satisfaction and quality of life outcomes, including burden, convenience, pain, and psychological well-being, were significantly higher with inhaled insulin treatment compared with SC insulin in patients with type 1 diabetes.¹⁴ Patient preference for this form of insulin therapy was further demonstrated in a study in which patients with type 1 or type 2 diabetes were allowed to switch therapies at the end of a 12-week randomized phase comparing inhaled insulin with subcutaneously injected human insulin. Eighty-five percent of patients who were randomized to inhaled insulin continued treatment, whereas only 13% switched to SC insulin. In the group randomized to SC insulin, only 21% continued treatment; whereas 76% switched to inhaled insulin.¹⁷ Treatment satisfaction scores were significantly higher among patients receiving inhaled insulin in both phases of this study.

Moreover, in a study of theoretical treatment choices among patients with type 2 diabetes failing

■ **Figure 2.** Pharmacokinetics of Different Forms of Insulin



NPH indicates neutral protamine Hagedorn.

Sources: References 4-6.

to achieve target glycemic control despite lifestyle and/or oral agent treatment, “the availability of inhaled insulin as a treatment option significantly increased the proportion of patients who would theoretically choose insulin overall. Patients were 3 times more likely to choose insulin therapy when inhaled insulin was available, and inhaled insulin was the most frequently chosen treatment option.”¹⁸

As with subcutaneously injected insulin, the most frequent adverse event with inhaled insulin is hypoglycemia. Frequency of hypoglycemia was similar in the clinical trials that compared inhaled and SC insulin.

The use of inhaled insulin is contraindicated in patients with unstable or poorly controlled lung disease and in those who smoke, including those who stopped smoking less than 6 months before consideration for treatment with Exubera. The use of Exubera in patients with underlying lung disease, such as

■ **Table.** Dose-dependent Pharmacokinetics of Insulin Detemir*

Parameter	Dose (U/kg)				
	0.1	0.2	0.4	0.8	1.6
Onset of action (h)	2.0	2.0	1.6	1.1	0.8
Time to peak (h)	3.2	6.2	8.6	9.3	8.7
Duration of action (h)	5.7	12.1	19.9	22.7	23.2

*Data shown are mean values.
Source: Reference 8.

asthma or chronic obstructive pulmonary disease, is not recommended, because the safety and efficacy of Exubera in this population have not been established. All patients should have spirometry (forced expiratory volume in 1 second [FEV₁]) assessed before initiating therapy. Assessment of lung diffusion capacity of carbon monoxide (DLCO) should be considered. Pulmonary function assessment should be repeated 6 months after initiation and annually thereafter.¹² During the 2-year clinical trials, declines from baseline FEV₁ of $\geq 20\%$ were observed in 1.5% of patients treated with inhaled insulin compared with 1.3% in the comparator group, and declines from baseline DLCO $\geq 20\%$ occurred in 5.1% of patients treated with inhaled insulin compared with 3.6% in the comparator group.¹²

Amylinomimetics

Amylin is a neuroendocrine hormone that is co-secreted with insulin from pancreatic beta cells in response to meals. Amylin inhibits postprandial glucagon secretion, slows the rate of gastric emptying, enhances satiety, and reduces food intake. Together, these amylin-mediated activities result in the suppression of postprandial glucose excursions.^{19,20} Because of the co-localization of amylin and insulin within beta cells, patients with type 1 diabetes have an absolute deficiency of both, whereas patients with type 2 diabetes have a relative deficiency of both hormones, including a markedly impaired amylin and insulin response to meals.²¹

Native amylin is insoluble and aggregates in solution, and therefore is not suitable for pharmacologic administration. The development of a soluble peptide analog of amylin, pramlintide, circumvented this difficulty and allowed clinical studies of amylin-based therapy.²² In 2005, pramlintide was approved by the FDA for use in patients with diabetes treated with mealtime insulin who have not achieved glycemic goals.²³

Clinical studies have shown that pramlintide treatment significantly reduces postprandial glucagon secretion in insulin-treated patients with type 1 or type 2 diabetes, leading to improved postprandial glycemic control.¹⁹ Sustained reductions in A1C levels are observed in response to pramlintide treatment, ranging from about 0.1% to 0.67% in patients with type 1 diabetes and from 0.3% to 0.62% in patients with type 2 diabetes.²² The most

frequent side effect of pramlintide is nausea, which is generally mild to moderate and diminishes over time. Higher doses are associated with a greater incidence of nausea.²² For this reason, pramlintide dosage is titrated on the basis of response and tolerability. Because pramlintide improves glycemic control and often results in decreased caloric intake, it has been associated with an increased incidence of insulin-induced hypoglycemia, particularly in patients with type 1 diabetes. Initial prandial insulin dose reductions, along with starting pramlintide at a low dose, are therefore required when initiating therapy.²³

Incretin-based Therapy

The Incretin Effect. In healthy nondiabetic subjects, oral administration of glucose produces a substantially enhanced insulin response compared with intravenous administration of glucose that results in a similar glucose excursion. This discrepancy has been called the *incretin effect*, and this effect is diminished in people with type 2 diabetes.²⁴ Subsequent studies identified 2 primary gut-derived hormones that are responsible for most of the incretin effect: glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1). GLP-1 is a better therapeutic target and has accordingly been studied to a greater extent.²⁵

GLP-1 inhibits postprandial glucagon release and stimulates glucose-dependent insulin secretion.^{26,27} This hormone also slows gastric emptying and enhances satiety.^{26,28} At least in animals, at the cellular level GLP-1 appears to stimulate beta cell growth and survival and reduce apoptosis, leading to increases in beta cell mass (**Figure 3**).²⁶⁻²⁹

Unfortunately, GLP-1 has an *in vivo* half-life of less than 2 minutes, which prevents it from being an attractive therapeutic candidate. The major metabolic pathway for GLP-1 is degradation by dipeptidyl peptidase-4 (DPP-4); this enzyme cleaves the NH-2 terminus of GLP-1 and related peptides, including GIP.³⁰ Two strategies have been pursued to allow therapeutic agents to circumvent this rapid degradation: incretin mimetics, which involve GLP-1 agonists or analogs that are resistant to DPP-4-mediated degradation, and DPP-4 inhibitors, that prolong the half-life of endogenous GLP-1.

Incretin Mimetics. The only currently available

incretin mimetic is exenatide (Byetta), a GLP-1 agonist that was approved by the FDA in 2005 as adjunctive therapy for patients with type 2 diabetes who are taking metformin and/or a sulfonylurea, or a TZD with or without metformin. Exenatide is a synthetic analog of exendin-4, a peptide found in Gila monster saliva, that binds to and activates the human GLP-1 receptor.^{25,31} In 30-week clinical trials, exenatide at a dose of 10 µg SC twice daily reduced A1C levels by a placebo-subtracted 0.9% to 1.0% in patients with type 2 diabetes who were receiving treatment with metformin and/or a sulfonylurea. These trials also reported a dose-dependent weight loss of 1.6 to 2.8 kg from baseline with exenatide at the 10-µg twice-daily dose.³²⁻³⁴

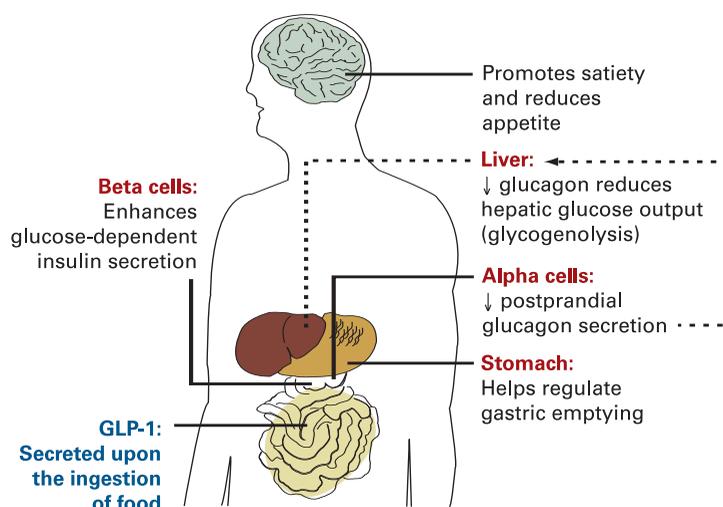
Patients who received exenatide in the original 30-week placebo-controlled trials were eligible for entry into a 1-year open-label extension trial. Long-term data from this study indicate that A1C reductions in response to exenatide were sustained over 82 weeks (30-week controlled trial + 1-year open-label extension). Greater A1C reductions are seen with higher baseline A1C levels (Figure 4), with reductions of 1.6% to 2% in patients with baseline A1C \geq 9%.³⁵

The sustained reductions in A1C may be related to the effects of exenatide on pancreatic beta cells. Consistent with the known activities of GLP-1, exenatide promotes beta cell proliferation and differentiation in animal models and also enhances beta cell function in patients with type 2 diabetes.³⁶

Weight loss did not plateau but continued throughout 82 weeks of exenatide treatment, with a mean reduction from baseline of 4.4 kg. Weight loss occurred in the absence of formal nutrition or exercise instructions and was not dependent on nausea. Improvements in other cardiovascular risk factors, including increases in high-density lipoprotein and decreases in diastolic blood pressure, were also observed.³⁵

Exenatide enhances endogenous insulin secretion in a glucose-dependent manner (ie, insulin secretion diminishes as glucose levels decrease into the normal range). This should reduce the risk for hypoglycemia with exenatide. As might be expected, exenatide in combination with metformin was associated with no greater incidence of hypoglycemia than exenatide plus placebo.³³ Additionally, under hypoglycemic conditions in healthy

■ **Figure 3.** Effects of Glucagon-like Peptide-1 (GLP-1) on Glucose Homeostasis



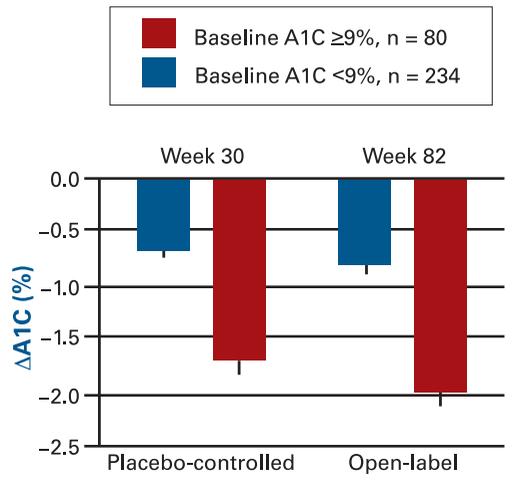
Sources: References 26-29.

controls, exenatide does not impair the counterregulatory response to hypoglycemia.³⁷ In contrast to the situation with exenatide, sulfonylurea-induced insulin secretion is not glucose-dependent, and increased rates of hypoglycemia have been observed when exenatide was added to the regimen of patients treated with sulfonylureas or sulfonylureas plus metformin.^{32,34}

Recently, exenatide received FDA approval for use in combination with a TZD. Exenatide decreased A1C by $-0.8 \pm 0.9\%$ from a baseline of $7.9 \pm 0.9\%$ when added to patients with type 2 diabetes not at goal despite treatment with a TZD alone or in combination with metformin. Improved glycemic control was not associated with a greater risk of hypoglycemia than placebo and was associated with a 1.5 ± 3.1 -kg weight change.³⁸ As with metformin, the mechanism of action of TZDs does not lead to hypoglycemia, which may make it possible to employ triple combination therapy without increasing the risk of hypoglycemia. Additionally, combination therapy may limit the weight gain often seen with TZD therapy.

Another incretin mimetic, liraglutide, is currently undergoing FDA regulatory trials. This compound is an acylated GLP-1 analog that is bound to albumin and has a half-life of about 12 hours.^{25,39,40} A once-daily injection of liraglutide was evaluated in a double-blind, placebo-controlled, randomized

■ Figure 4. Baseline-dependent Glycosylated Hemoglobin (A1C) Reductions in 314 Patients Treated With Exenatide in Addition to Sulfonyleurea and/or Metformin



For patients with baseline A1C $\geq 9\%$, mean baseline A1C = 9.7%.

For patients with baseline A1C $< 9\%$, mean baseline A1C = 7.8%.

Source: Reference 35.

trial in patients with type 2 diabetes. At the highest liraglutide dose (0.75 mg), A1C reductions of 0.75% were recorded at 12 weeks; this decrease was almost identical to that observed in the open-label comparator arm in which patients received glimepiride (0.74% reduction).⁴¹ Liraglutide was also effective in improving glycemic control in metformin-treated patients (A1C reduction of 0.8% over 5 weeks).⁴² As with exenatide, liraglutide has been reported to enhance beta cell function⁴³ and is associated with decreases in body weight.^{41,42}

DPP-4 Inhibitors. The most recent agent to be approved by the FDA for the treatment of type 2 diabetes is sitagliptin (Januvia), an oral, once-daily DPP-4 inhibitor that can be given alone or in combination with metformin or a TZD.⁴⁴ Sitagliptin-mediated inhibition of DPP-4 results in an approximately 2- to 3-fold increase in endogenous GIP and GLP-1 levels.⁴⁴ A1C reductions of 0.65% were reported when sitagliptin was administered to metformin-treated patients,⁴⁵ whereas monotherapy was associated with placebo-subtracted A1C reductions of 0.79% to 0.94%.⁴⁶ Sitagliptin-mediated effects were dependent on baseline A1C; patients with baseline levels $\geq 9\%$ showed placebo-subtracted A1C reductions of

1.5% with sitagliptin monotherapy. A1C reductions were accompanied by improvements in measures of beta cell function.⁴⁶

Sitagliptin is primarily eliminated via renal excretion, and 2- to 4-fold increases in plasma levels have been observed in patients with moderate-to-severe renal insufficiency. For this reason, renal function testing should be performed before initiation of sitagliptin therapy and periodically during treatment. Dosage adjustments are recommended in patients with moderate renal insufficiency and in patients with severe renal insufficiency or with end-stage renal disease requiring hemodialysis or peritoneal dialysis.⁴⁴

Vildagliptin (LAF237) is another oral DPP-4 inhibitor currently in phase 3 trials. Vildagliptin at a dose of 50 mg once daily was added to ongoing metformin in a double-blind, placebo-controlled, randomized trial of patients with type 2 diabetes. In the vildagliptin arm, A1C levels decreased by 0.6% over 12 weeks; sustained reductions were observed in the 40-week extension study. However, during that time A1C levels in the placebo group continued to rise, resulting in a between-group difference of 1.1% after 1 year. Weight reductions in the placebo and vildagliptin arms were comparable at 12 weeks and identical (-0.2 kg) at 1 year.⁴⁷ A separate study reported that vildagliptin improved beta cell function in patients with type 2 diabetes by increasing the insulin secretory rate.⁴⁸

Management of Type 2 Diabetes in the Future

The choice of diabetic therapies will likely continue to expand in the coming years. Additional insulins to be delivered by pulmonary inhalation and other noninjection delivery systems are under development and/or in trials. Other oral antihyperglycemic agents are also being investigated.

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