

Commentary

New Developments in Diabetes Management: Medications of the 21st Century

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ABSTRACT

Background: Suboptimal blood glucose control among patients with type 2 diabetes continues to support the need for new pharmacologic approaches.

Objective: The purpose of this commentary was to highlight newly available and soon-to-be available agents that are promising tools for targeting specific pathophysiologic pathways in the management of diabetes.

Methods: Published evidence to support the application of novel incretin-based therapies, dipeptidyl peptidase (DPP)-4 inhibitors, sodium-glucose cotransporter (SGLT)-2 inhibitors, other oral agents and insulins for managing specific aspects of type 2 diabetes, as well as disadvantages associated with those novel medications, are discussed.

Results: Several new glucagon-like peptide (GLP)-1 receptor agonists with different time frames of action, although each has unique advantages and disadvantages, have been through clinical trials. Examples of these are lixisenatide and albiglutide. Currently available DPP-4 inhibitor agents, important for inhibiting the breakdown of endogenous GLP-1, have not been associated with weight gain or hypoglycemia. SGLT-2 inhibitors, which do not depend on insulin secretion or insulin action, may be advantageous in that they appear to be broadly efficacious at all stages of diabetes. New insulin analogues, such as degludec and U-500, improve glycemic control without contributing to hypoglycemia.

Conclusions: Advances in pharmacologic options offer the promise of improving glycemic control for longer periods, with limited glycemic fluctuations, hypoglycemia, and weight gain. However, the effectiveness

of these agents ultimately depends on their availability to providers managing the health care of patients at high risk for poor diabetes outcomes and patients' use of them as directed. Long-term effectiveness and safety trials are ongoing. (*Clin Ther.* 2014;36:477–484) © 2014 Elsevier HS Journals, Inc. All rights reserved.

Key words: Diabetes Treatment, Glucagon-like Peptide 1, DPP-4 inhibitors, Incretins, Sodium -glucose co transporter 2 (SGLT2) inhibition, Novel Insulins.

INTRODUCTION

Despite considerable advances in the therapy for type 2 diabetes, blood glucose control remains suboptimal.¹ Physicians and others who are struggling to prevent and minimize diabetes complications among their patients continue to face a number of challenges. A significant component of diabetes management lies with the person with diabetes.² Diabetes self-management includes using prescribed medications as recommended by the diabetes clinician; however, medication nonadherence may be caused, in part, by the medications themselves, including weight gain, unpredictable glucose fluctuations in the postprandial period, and plunges in glucose levels causing hypoglycemic events. Although multifactorial in nature,³ medication nonadherence may also be caused by comorbidities of diabetes, including cognitive impairment and depression, as well as financial constraints. Providers managing type 2 diabetes are challenged in their efforts to sustain blood glucose at goal for the long term while also reducing or eliminating the residual risk for cardiovascular events,^{4–6} despite important

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Table 1. The Ominous Octet—pathophysiologic abnormalities (and treatment targets) contributing to hyperglycemia in type 2 diabetes.⁹

1. Decreased insulin secretion
2. Decreased glucose uptake in tissues due to insulin resistance
3. Increased hepatic glucose production
4. Decreased incretin effect
5. Increased glucagon secretion (and lack of suppression during hyperglycemia)
6. Increased lipolysis and free fatty acids in circulation
7. Neurotransmitter dysfunction
8. Increased glucose reabsorption in the renal tubule

advances in preventive cardiology. Health care systems contribute to the challenges of mitigating the long-term societal costs of an increasing proportion of the population that is living with diabetes and its complications. Systems struggling to manage increasing volumes of patients with diabetes and their multimorbidities have inadequately invested in diabetes self-management resources⁷ and inadequately adopted next-generation diabetes medications by integrating them into their formularies.⁸

Several abnormalities have been identified in the pathophysiology of type 2 diabetes, and at least 8 of them (**Table 1**) are amenable to treatment, serving as pharmacologic targets.⁹ The purpose of this review is to highlight some recent therapies that have become available for the treatment of type 2 diabetes or that are expected to become available in the near future, while placing them within the diabetes treatment algorithm, targeting pathophysiology appropriately. The medication classes that are addressed here include glucagon-like peptide (GLP)-1 agents, dipeptidyl peptidase (DPP)-4 inhibitors, sodium-glucose cotransporter (SGLT)-2 inhibitors, insulins, and other agents still under investigation.

INCRETIN-BASED THERAPIES

In the past 3 decades, several studies have demonstrated that insulin secretion is greater following an oral glucose load compared with intravenously administered glucose.¹⁰ This incremental increase in

insulin secretion from glucose or food is mediated through signals from the gut. This process has been termed the *incretin effect*. Several incretins have been identified, with GLP-1 most likely the most important. GLP-1 is a natural hormone secreted in the gut that has been used in physiologic studies.¹⁰

The incretin effect is attenuated in people with diabetes and has been considered an important abnormality that can now be corrected with drug therapy. An infusion of GLP-1 leads to a reduction in glucose with a stimulation of insulin secretion and suppression of plasma glucagon in a glucose-dependent manner, suggesting that insulin secretion is no longer stimulated and that glucagon secretion increases when blood glucose is reduced to the normal range. This process represents an important defense mechanism against hypoglycemia and is an advantage of GLP-1–related therapies in the treatment of diabetes. In contrast, sulfonylureas continue to stimulate insulin secretion even when in the presence of hypoglycemia. This important difference between treatments has been confirmed in several clinical trials.^{11,12}

GLP-1 has a very short half-life, as a result of the enzyme dipeptidyl peptidase (DPP)-4, a naturally occurring enzyme that is present in most tissues of the body and that naturally breaks down GLP-1.^{12,13} Due to the short half-life, natural GLP-1 would need to be administered by continuous infusion. Because this is generally impractical, the pharmacologic approach to replace GLP-1 consists of either using an analogue that is resistant to DPP-4, leading to a longer half-life, or administering pharmacologic agents that inhibit the activity of the enzyme DPP-4.

The first GLP-1 analogue or receptor agonist to become available was exenatide, which is actually an analogue of exendin-4 (with others in development).^{11,14,15} A long-acting version of this compound, consisting of microspheres within a biodegradable polymer, is available for once-weekly dosing. An alternative approach is an analogue of human GLP-1, which has been slightly modified to add on the fatty acid that binds to albumin. The albumin analogue complexes are resistant to DPP-4, and free GLP-1 is gradually released from this complex. Liraglutide (which is effective for 24 hours) is an example of this approach,^{16,17} and others are in development.

GLP-1 receptor agonists have several clinical effects, listed in **Table II**. They increase insulin secretion and decrease glucagon production, leading to

Table II. Potential clinical effects of GLP-1 receptor agonists.**Physiologic effects**

- Increased GLP-1 activity
 - Decreased glucagon production
 - Increased insulin synthesis and secretion
- Glycemic control
 - Decreased A_{1c}
 - Decreased FPG and PPG
- Weight effects
 - Decreased gastric emptying
 - Decreased caloric intake
 - Weight loss

Potential clinical advantages

- Low to no hypoglycemia
- Weight reduction
- Potential for improved β -cell mass/function?
- Potential cardiovascular protective actions?

Potential clinical disadvantages

- Gastrointestinal side effects
- Injectable
- Training requirements
- High cost

A_{1c} = hemoglobin A_{1c}; FPG = fasting plasma glucose; GLP-1 = glucagon-like peptide-1; PPG = postprandial plasma glucose.

improved glucose control. In addition, they decrease gastric emptying, which delays food absorption and may have an effect on appetite, leading to weight loss. The GLP-1 agonist is not associated with hypoglycemia and weight loss, suggesting important clinical advantages to using this agent.¹⁶ Further, data suggest a potential to improve β -cell function over the long term and prevent the decline of natural progression of β -cell loss. On the other hand, they have several disadvantages, including the need for injections that require training, frequent gastrointestinal side effects, and a high cost. Other GLP-1 receptor agonists are in development, both short acting, such as lixisenatide, and long acting, such as albiglutide. Differences between agents are related to their pharmacokinetic properties (short- vs long-acting agents given weekly) or to plasma levels of free drug able to stimulate the receptor, which may determine side effects. For example, once-weekly preparations of exenatide cause less nausea and vomiting than do

shorter-acting agents such as exenatide or liraglutide. Understanding such differences may help a clinician to individualize therapy for the patient.

The American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) Position Statement recommends a GLP-1 receptor agonist as an initial drug therapy in patients in whom metformin is contraindicated (eg, in patients with moderate renal impairment) or cannot be tolerated and in whom weight loss is essential.¹⁸ Alternatively, it can be used as second- or third-line therapy in combination with metformin or other agents.

Table III¹⁹ compares short- and long-acting GLP-1 receptor agonists, which may have differences beyond the duration of action that may be clinically relevant. For example, the short-acting agonists have a powerful effect on postprandial hypoglycemia compared with the long-acting ones, mainly through an effect on gastric emptying. This has potential advantages if these drugs are combined with basal insulin.

A number of clinical trials have tested GLP-1 receptor agonists, including exenatide,²⁰ liraglutide,²¹ and lixisenatide,¹⁴ in combination with basal insulin. Ongoing clinical trials are evaluating the potential for combining a GLP-1 receptor agonist with basal insulin in the same injection device.^{22,23}

The major advantage of GLP-1 receptor agonists is lowering body weight, which can be substantial in some patients, although it is unpredictable. The weight appears to be mainly visceral fat, and there are other benefits, including reductions in blood pressure.

A number of concerns have been raised about GLP-1 receptor agonists, including an increased risk for pancreatitis, and the US Food and Drug Administration (FDA) recommends that the drug not be used in patients who have a history of pancreatitis. However, the true propensity to cause pancreatitis is unclear. Drugs may also induce antibody formation (particularly with exendin-based drugs), although the clinical significance of this activity is unclear.

DPP-4 Inhibitors

As incretin agents, DPP-4 inhibitors enhance the duration of action of endogenous GLP-1 by blocking its breakdown. Studies have suggested that even in the long term they continue to suppress glucagon.^{22,24} Several DPP-4 inhibitors are currently available (eg, sitagliptin, saxagliptin, alogliptin, linagliptin), all of which apparently are similar with regard to efficacy

Table III. Comparison of short- and long-acting GLP-1 receptor agonists.¹⁹

Parameter	Short Acting	Long Acting
Compounds	Exenatide, lixisenatide	Albiglutide, dulaglutide, exenatide-LAR, liraglutide
Half-life	2–5 h	12 h to several days
Effects		
FBG reduction	Modest	Strong
PP hyperglycemia reduction	Strong	Modest
Fasting insulin secretion stimulation	Modest	Strong
PP insulin secretion	Reduction	Modest stimulation
Glucagon secretion	Reduction	Reduction
Gastric emptying rate	Deceleration	No effect
Weight reduction, kg	1–5	2–5
Induction of nausea, %	20–50, attenuates over weeks to months	20–40, attenuates over 4–8 wks

FBG = fasting blood glucose; GLP-1 = glucagon-like peptide-1; LAR = long-acting release; PP = postprandial. Adapted by permission from Macmillan Publishers Ltd: Nature Reviews Endocrinology, GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus, copyright 2012.

and tolerability, although they have different sites of breakdown and metabolism. Linagliptin is different from other DPP-4 inhibitors in that it is not excreted through the kidney and therefore may be used in patients with renal impairment without lowering the dose.

Overall, this class of drugs has modest effects on glycemia; however, there are still advantages to using them, including ease of administration using the oral route, good tolerability, and a lack of association with weight gain or hypoglycemia. They are therefore preferentially used over sulfonylureas in patients who fail on metformin monotherapy, who have modest elevations in A_{1c} , and in whom it is important to avoid side effects, especially hypoglycemia.

A number of cardiovascular outcomes trials have been conducted with incretin agents, 2 of which have recently completed.^{25,26} Contrary to study expectations based on a reduction in events from meta-analysis of short-term clinical trials, neither study demonstrated a reduction in events. The outcomes from these studies serve to reiterate the importance of engaging in specific cardiovascular outcomes trials rather than relying on short-term trial data. Furthermore, data from the SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus) trial²⁵ suggest an increase in hospitalization for heart failure with saxagliptin compared with placebo. This

intriguing finding may have occurred by chance but requires additional study. Several other trials are ongoing, with an incretin drug or placebo added on to usual therapy. The latter may differ between groups and lead to the confounding of differences in glycemic control or hypoglycemia. Indeed, in a study of linagliptin compared with sulfonylurea in combination with metformin over 1 year, glycemic control was similar but cardiovascular events were fewer in the linagliptin-treated group.²⁷ This result needs to be confirmed in a larger and longer trial.

Sodium-Glucose Cotransporter 2 Inhibitors

The sodium-glucose cotransporter (SGLT)-2 is involved in reabsorbing 90% of glucose that is filtered in the glomerulus of the kidney.²⁸ Most of this resorption occurs in the proximal renal tubule, resulting in a minimal amount of glucose—if any—excreted in the urine. However, in diabetes, this transporter is saturated and glycosuria occurs, although it may occur at a higher level of blood glucose than in healthy individuals, perhaps due to a maladaptive process.²⁸ By blocking this transporter, a number of drugs have been shown to increase glycosuria and have been developed for the treatment of type 2 diabetes.^{28,29} They cause loss of glucose in the urine, thereby contributing to falling

Table IV. Potential advantages of and concerns about SGLT-2 inhibitors.

Potential Advantages	Concerns
Once-daily administration	Bacterial urinary tract infections
Decreases FPG, PPG, A _{1c}	Fungal genital infections
Weight loss (60 g urine glucose = 240 kcal/d = 0.5 lb/wk)	May not be as effective in patients with renal impairment
No/low risk for hypoglycemia	Rise in LDL-C
Modest blood pressure lowering	Cancer in dapagliflozin trials
Effect independent of insulin secretion or insulin resistance	Transient initial period of dehydration, polyuria, thirst
Use complementary with other type 2 diabetes treatments	No known long-term effects on kidney or on CV outcomes
Potential for use in type 1 diabetes	Added cost to diabetes therapy

A_{1c} = hemoglobin A_{1c}; CV = cardiovascular; FPG = fasting plasma glucose; LDL-C = low-density lipoprotein cholesterol; PPG = postprandial glucose; SGLT-2 = sodium-glucose cotransporter 2.

blood glucose levels. Canagliflozin and dapagliflozin have been shown to lower A_{1c} by ~0.8%.^{30–33}

Table IV illustrates the potential advantages and disadvantages of SGLT-2 inhibition. They are easy to use and have the advantage of working on all phases of glucose metabolism, with no risk for hypoglycemia. They also cause modest blood pressure lowering and weight loss and work in combination with all other treatments for diabetes. However, by increasing the amount of glucose in the genitourinary tract, fungal genital infections may occur in some individuals.

The exact role of SGLT-2 inhibitors in the diabetes treatment algorithm remains to be determined. The drugs became available only after the publication of the ADA/EASD guidelines and were therefore not discussed therein. Nonetheless, clinical trials have demonstrated their efficacy at all stages of diabetes, including the late stage of patients treated with insulin in combination with oral agents.³⁴ This broad efficacy and synergy perhaps relate to the unique mechanism of action that is different from that of all other agents and is not dependent on insulin secretion or activity.

INVESTIGATIVE AGENTS IN TYPE 2 DIABETES

Several new therapies have been developed for the treatment of type 2 diabetes and are summarized in **Table V**. Closest to the market are several long-acting GLP-1 receptor agonists, several SGLT-2 inhibitors, as well as some dual inhibitors, and activators of

G-protein-coupled receptor (GPR)-40, a receptor that is present on the surface of β cells.³⁵ In addition, inflammation has been identified as a target for the treatment of diabetes, and several anti-inflammatory agents have been shown to improve glucose control.^{36–38}

Salsalate, a treatment of rheumatoid arthritis, was shown to be modestly effective in patients with type 2 diabetes in a 12-month randomized trial. However, there were small increases in both albuminuria and low-density lipoprotein cholesterol. The mechanism for these increases was unclear. Antibodies to interleukin-1 have also been shown to have glucose-lowering properties and may be developed for the treatment of type 2 diabetes.³⁹ Finally, the GPR-40 agonist TAK-875 has been shown to be as effective as glimepiride in lowering glucose, but caused less hypoglycemia, in a head-to-head trial.³⁵ However, development of this compound was recently discontinued due to hepatic toxicity. Finally, an inhibitor of the enzyme 11 β -hydroxysteroid dehydrogenase has also been shown to reduce A_{1c} significantly,⁴⁰ but concerns remain about interference with the pituitary-adrenal axis.

INSULIN

There have been several developments in insulin therapy in the past few decades with the development of insulin analogues. These analogues have been shown to improve glycemic control, with less hypoglycemia, in several studies.⁴¹

Table V. Investigational agents being developed for the treatment of type 2 diabetes mellitus.

Long-acting glucagon-like peptide-1 (GLP-1) receptor agonists
Sodium-glucose cotransporter (SGLT) -1 and -2 inhibitors
Ranolazine
Dual (α/Γ) & Pan ($\alpha/\Gamma/\Delta$) peroxisome proliferator-activated receptor (PPAR) agonists
11 β hydroxysteroid dehydrogenase (HSD)-1 inhibitors
Fructose 1,6-bisphosphatase inhibitors
Glucokinase activators
G protein-coupled receptor (GPR)-40 and -119 agonists
Protein tyrosine phosphatase (PTB)-1b inhibitors
Carnitine palmitoyltransferase (CPT)-1 inhibitors
Acetyl coenzyme A carboxylase (ACC)-1 and -2 inhibitors
Glucagon receptor antagonists
Salicylate derivatives
Immunomodulatory drugs

New basal insulin analogues have been developed, with several of them, such as degludec, having been approved in countries other than the United States. Degludec has been shown to be longer acting than insulin glargine.⁴² Studies of degludec suggest that it may cause less nocturnal hypoglycemia than glargine.⁴³ The US FDA has asked the manufacturer to complete a long-term study of cardiovascular outcomes with insulin degludec before making a safety determination. Another basal insulin analogue, pegylated insulin lispro, has specific activity on the liver, with theoretical potential for less weight gain than with other basal insulins - that needs to be confirmed in clinical trials. Patients in clinical trials of pegylated insulin lispro experienced less weight gain than with other basal insulins. In a clinical trial of degludec plus aspart insulin as basal bolus therapy compared with glargine plus aspart in patients with both type 1 and type 2 diabetes, efficacy was similar, but nocturnal hypoglycemia was less with degludec.^{42,43} Several very rapid-acting insulin analogues are in development, including insulin mixed with hyaluronidase to enhance its absorption.

Finally, there has been an increase in the use of more concentrated insulins, such as U-500 insulin, which has a pharmacokinetic profile different from that of regular insulin U-100. The reason for the change of pharmacodynamic properties is not clear. Nonetheless, concentrated insulins, such as U-200 degludec and U-300 glargine, continue to be developed because some patients have very high insulin requirements.⁴⁴

Coupled with advances in insulin therapy, there have been developments in continuous glucose-monitoring systems, which, when used together with pump therapy, have been shown to reduce the risk for hypoglycemia, particularly when a signal to a pump to switch off for a short period of time when the blood glucose is dropping may be very useful in treating type 1 diabetes.⁴⁵ Such a pump coupled with continuous glucose-monitoring systems has been approved by the FDA for clinical use.

Although islet-cell transplants are effective in the short term, other treatments for type 1 diabetes have been somewhat disappointing. A number of immunotherapies for type 1 diabetes have been tried but so far have been shown to have a transient effect. There remains interest in stem cell therapy for type 1 diabetes; stem cell therapy has been explored for type 2 diabetes as well.⁴⁴

CONCLUSIONS

We have made tremendous progress with the management of diabetes. However, the disease remains a challenge because of its very high prevalence as well as disease progression and associated comorbidities. Several novel approaches have been tried to help overcome the burden of diabetes, targeting novel pathways that promise to improve diabetes control and eliminate long-term complications.

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CONFLICTS IN INTEREST

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