

SUPPLEMENT TO

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**THE ROLE OF INCRETIN-BASED THERAPIES
IN TREATING PATIENTS WITH
TYPE 2 DIABETES MELLITUS**

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CLEVELAND CLINIC

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THE ROLE OF INCRETIN-BASED THERAPIES IN TREATING PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Incretin-based therapies for type 2 diabetes mellitus: New therapeutic mechanisms

Almost a decade into the 21st century, the global epidemic of diabetes—which accelerated in the 1970s—shows no sign of slowing. At the same time, our insights into both type 1 and type 2 diabetes mellitus (T2DM) have increased at a similarly rapid rate.

At the beginning of the 1970s, it was far from clear whether improved glycemic control made much difference in the long-term well-being of people with diabetes other than to relieve their symptoms of hyperglycemia and decrease the likelihood of diabetic ketoacidosis or hyperglycemic hyperosmolar nonketotic coma. Concerns were expressed about the risk/benefit ratio of antihyperglycemic drugs—so there is nothing new under the sun! The drugs available in the United States were limited to insulin and sulfonylureas. The rest of the world also had access to metformin, but, in truth, its potential was underestimated until much later.

■ RECOGNIZING THE VALUE OF GLYCEMIC CONTROL

Out of this milieu of scientific uncertainty grew the two clinical trials that effectively ended the debate about the value of glycemic control: the Diabetes Control and Complications Trial (DCCT)¹ for type 1 diabetes, and the United Kingdom Prospective Diabetes Study (UKPDS)^{2,3} for T2DM. The conduct of these trials was facilitated by the timely demonstration of the utility of glycosylated hemoglobin (HbA1c) as an objective measure of glycemic control, and of microalbuminuria as a marker of early nephropathy.

Both the DCCT and the UKPDS, in their initial “end of study” analyses in the 1990s, established the role of glycemic control in reducing the risk of retinopathy, neuropathy, and nephropathy—the microvascular complications of diabetes. Additionally, the UKPDS demonstrated that in T2DM, hypertension management was at least as important as glycemic control in reducing the risk of microvascular complications.

Neither the DCCT nor the UKPDS was powered to determine initially whether glycemic control was a risk factor for cardiovascular disease; however, careful

longer-term surveillance of the patient cohorts in the studies has recently borne fruit in this regard. Reports from both studies have shown that efforts to control glycemia early in the course of diabetes are rewarded many years later by a decreased risk of cardiovascular events and death.^{4,5} This is true even when excellent glycemic control achieved early on is not sustained indefinitely. It has also become widely recognized that the management of diabetes, with prevention of microvascular and cardiovascular disease as major aims, involves much more than a simple preoccupation with glycemic control—important as that is.

■ NEW TREATMENT OPTIONS

Concurrent with the DCCT and the UKPDS being conducted with, in effect, the therapeutic tools of the 1970s, considerable strides were being made in the development of new classes of antihyperglycemic agents for use in T2DM. These include the thiazolidinediones (TZDs), alpha-glucosidase inhibitors, nonsulfonylurea insulin secretagogues (also known as glinides), and, more recently, the incretin-based drugs that are the focus of this supplement to the *Cleveland Clinic Journal of Medicine*.

Understandable enthusiasm for tapping into the hitherto unexploited pathways and mechanisms targeted by a new drug class is inevitably tempered by known, or sometimes unforeseen, adverse effects. Some of the adverse effects typically associated with antihyperglycemic drugs used before the incretin-based therapies became available include hypoglycemia, weight gain, and fluid retention; all of these are perceived as possibly increasing the risk of the very thing we are striving to avoid in diabetes—cardiovascular morbidity and mortality. Such is the concern about this risk—epitomized, rightly or wrongly, in the controversial meta-analysis of clinical trials involving rosiglitazone⁶—that the US Food and Drug Administration now requires new antihyperglycemic drugs not only to meet efficacy standards for improving glycemia but also to show no sign of increased cardiovascular risk. The requirement must be met in preapproval trials, to be followed by postmarketing studies to prove the lack of cardiovascular risk.

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As the contributions in this supplement point out, incretin-based therapies generally are either weight neutral or promote weight loss; by their modes of action, they are unlikely to cause hypoglycemia; and, as shown thus far, they are unassociated with fluid retention or increased likelihood of heart failure. Continued vigilance regarding cardiovascular risk will be important for the new incretin-based therapies, however.

■ BETA-CELL FUNCTION STILL A CHALLENGE

Another aspect of T2DM highlighted by the UKPDS is the degree of pancreatic beta-cell function loss—typically about 50% or more—at the time of clinical diagnosis, and the steady decline in function thereafter.⁷ This, as much as the understandable fatigue with lifestyle modification that normal humans experience, accounts for the frequent failure of oral antihyperglycemic monotherapy or dual therapy to maintain satisfactory glycemic control over the years. Relieving hyperglycemia at the time of diagnosis by any means usually leads to a temporary improvement in beta-cell function, but the possibility of slowing or even reversing the long-term decline has been an elusive therapeutic goal.

Although direct quantitative assessment of beta-cell function in humans is difficult in routine practice or outside of strict research protocols, a randomized study comparing different monotherapies for T2DM showed that over several years, the rise in HbA1c was more gradual with rosiglitazone than with glyburide or metformin; this suggests that, at least compared with metformin and sulfonylureas, the TZDs may have some longer-term benefit with respect to beta-cell function.⁸

That incretin-based treatments may help preserve or improve beta-cell function has been suggested by animal data.⁹ Proving that that is the case in humans will be much more challenging. A recent randomized study in patients with T2DM already taking metformin showed that addition of exenatide for 1 year resulted in improved beta-cell function, assessed by C-peptide responses to glucose and to arginine during a combined euglycemic-hyperinsulinemic and hyperglycemic clamp procedure. The improvement was evident compared with baseline function and with patients randomized to receive insulin glargine in addition to metformin for a year.¹⁰ However, 4 weeks after exenatide and glargine were discontinued, the beta-cell function had reverted to the pretreatment level and was not significantly different in the two groups of patients. Moreover, 3 months after treatment discontinuation, the HbA1c levels, which had decreased during the year to a similar extent in both groups, had returned to pretreatment levels. The investigators

acknowledged that it was impossible in their study to “discriminate between acute and long-term effects of exenatide on beta-cell function.”¹⁰ So, in my opinion, the challenge remains to show that meaningful long-term effects on beta-cell function can be achieved with incretin-based therapy.

That said, there is no doubt that the incretin-based therapies bring a new dimension to our ability to treat diabetes. The articles in this supplement will provide both the specialist and nonspecialist with a better understanding of these relatively new therapies.

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Current antihyperglycemic treatment strategies for patients with type 2 diabetes mellitus

■ ABSTRACT

The current epidemics of excessive weight and type 2 diabetes mellitus (T2DM) cause significant morbidity and mortality. T2DM frequently coexists with excess weight as well as hypertension and dyslipidemia, placing a significant percentage of the population at an elevated risk of cardiovascular disease. Maintaining effective glycemic control is linked with a diminished risk of developing microvascular complications, and recent studies have shown it may also reduce overall macrovascular complications. Reduction of associated risk factors, including those related to excessive weight, high blood pressure, and dyslipidemia, are also necessary to meaningfully decrease cardiovascular risk. Agents that can improve glycemia with weight neutrality or weight loss could offer additional benefit to overweight patients with T2DM. Although the major pathophysiologic defects in T2DM are recognized to be beta-cell dysfunction and peripheral insulin resistance, derangements in the incretin system may contribute as well. Antidiabetes agents targeting this system include dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists. Both classes have been shown to significantly reduce hyperglycemia. GLP-1 receptor agonists also promote significant weight loss and have potentially beneficial effects on cardiovascular risk markers.

■ KEY POINTS

Up to 65% of deaths among people with diabetes are caused by cardiovascular disease.

Glycemic control can delay or slow the progression of microvascular complications.

In addition to hyperglycemia, comprehensive diabetes therapy must target cardiovascular disease-related risk factors, including excess weight/obesity, elevated blood pressure, and abnormal lipid concentrations.

Diminished incretin hormonal activity contributes to the pathophysiology of diabetes.

Data from the Centers for Disease Control and Prevention indicate that almost 24 million Americans, or 7.8% of the population, have diabetes; 90% to 95% of these have type 2 diabetes mellitus (T2DM).¹ Diabetes and excessive weight often coexist. An analysis of data from the 1999–2002 National Health and Nutrition Examination Survey (NHANES) showed that among individuals with diabetes, 85% were overweight or obese and 55% were obese.²

Gaps remain in the management of T2DM between the goals for clinical parameters of care (eg, control of glucose, blood pressure [BP], and lipids) and actual clinical practice.³ NHANES data reveal that glycemic control improved from a mean glycosylated hemoglobin A1c (HbA1c) of 7.82% in 1999–2000 to 7.18% in 2003–2004.⁴ Hazard models based on the United Kingdom Prospective Diabetes Study (UKPDS) 10-year outcomes data in 4,320 newly diagnosed T2DM patients suggest that a sustained decrease in HbA1c of 0.511 percentage points could reduce diabetes complications by 10.7%.^{4,5}

Additional analysis of NHANES data showed that in 2003–2004, about 57% of individuals achieved glycemic control, 48% reached BP targets, and 50% achieved target cholesterol goals. Only about 13% of diabetes patients achieved their target goals for all three parameters concurrently.⁶

This article reviews the association between cardiometabolic risk and the current antihyperglycemic treatments for patients with T2DM, with a focus on the role of incretin-related therapies.

■ THE IMPORTANCE OF CARDIOMETABOLIC RISK IN T2DM

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality among people with diabetes and is the reported cause of mortality in up to 65% of deaths in persons with diabetes in the United States.⁷ The risk of CVD is two- to fourfold greater among adults with diabetes than among adults who do not have diabetes.⁸ The risk of CVD in patients with T2DM was evident in the UKPDS 17, where macrovascular complications, including CVD, were about twice as common as microvascular complications (20% vs 9%) after 9 years

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of follow-up.⁹ A study that involved more than 44,000 patients showed an almost double rate of mortality from all causes among individuals with T2DM compared with those with no diabetes (hazard ratio, 1.93; 95% confidence interval, 1.89 to 1.97).¹⁰ Current guidelines recommend aggressive management of CV risk factors, including BP control, correction of atherogenic dyslipidemia, glycemic control, weight reduction for those who are overweight or obese, and smoking cessation for those who smoke.^{3,11} Lifestyle interventions, including weight reduction and appropriately prescribed physical activity, result in reduced CV risk factors, which can help slow the progression of T2DM.¹²

■ GOALS OF T2DM THERAPY

Several studies have demonstrated that glycemic control can delay or prevent the development and progression of microvascular complications.^{13,14} UKPDS 33 showed that more intensive blood glucose control (median HbA1c 7.0%) in patients with T2DM followed over 10 years significantly ($P = .029$) reduced the risk for any diabetes-related end point by 12% compared with conventional therapy (median HbA1c 7.9%). Most of the risk reduction was accounted for by a 25% risk reduction in microvascular end points ($P = .0099$).¹³ Another report (UKPDS 35) demonstrated that HbA1c was strongly related to microvascular effects, with a 1% reduction in HbA1c associated with a 37% reduction in microvascular complications.¹⁴

Does intensive glucose control reduce CV risk?

To resolve the ongoing question of whether intensive glucose control can lead to a reduction in CV risk in patients with T2DM, three large, long-term trials were conducted within the last decade.^{15–18} Two of these, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) and Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE) trials, each enrolled more than 10,000 previously treated patients with long-standing T2DM. Patients were randomized to standard or intensive glycemic control for 3.5 years in the ACCORD trial and for 5 years in the ADVANCE trial.^{15,16}

The ACCORD and ADVANCE trials, along with the smaller Veterans Administration Diabetes Trial (VADT) ($N = 1,791$), failed to show that more intensive glycemic control significantly reduced CVD.^{15–17} Additionally, the glycemic control component of ACCORD was halted because of increased mortality in the intensive arm compared with the standard arm.¹⁵ Further analyses of ACCORD data presented at the 69th Scientific Sessions of the American Diabetes Association (ADA) showed that HbA1c values lower than 7.0% did not explain the increased mortality. The 20% higher risk of death for every 1.0% increase in HbA1c greater than

6.0% suggests that glucose concentrations even lower than the general HbA1c goal of less than 7.0% may be appropriate in some patients.¹⁸ The most recent finding from VADT was that CV risk was dependent on disease duration and presence of comorbidities. Intensive therapy seemed to work best in patients with diabetes of less than 15 years' duration, while risk of a CV event was more than doubled with intensive therapy in patients having diabetes for more than 21 years.

Clarification of treatment goals

A position statement of the ADA and a scientific statement of the American College of Cardiology Foundation and the American Heart Association¹⁹ concluded that the “evidence obtained from ACCORD, ADVANCE, and VADT does not suggest the need for major changes in glycemic control targets but, rather, additional clarification of the language that has consistently stressed individualization.” They state that while the general HbA1c goal of less than 7.0% seems reasonable, even lower HbA1c goals may be appropriate for some patients if they can be achieved without significant hypoglycemia or other adverse effects. Such patients might include those with diabetes of short duration, long life expectancy, or no significant CVD or hypoglycemia. Conversely, higher HbA1c goals may be appropriate for patients with limited life expectancy, a history of severe hypoglycemia, established microvascular or macrovascular complications, significant other comorbid conditions, or longstanding diabetes in whom an HbA1c of less than 7.0% has been difficult to attain despite optimal treatment and diabetes self-management education.¹⁹

Long-term risk reduction

A 10-year, postinterventional follow-up study (UKPDS 80) of the UKPDS survivor cohort was reported recently.²⁰ Results showed that despite an early loss of glycemic differences between patients treated with diet and those treated with intensive regimens (sulfonylurea or insulin; metformin in overweight patients), the pharmacotherapy group demonstrated a prolonged reduction in microvascular risk as well as a significant reduction in the risk for myocardial infarction (15% [$P = .01$] in the sulfonylurea-insulin group and 33% [$P = .005$] in the metformin group) and death from any cause.²⁰ This suggests that early improvement in glycemic control is associated with long-term benefits in the micro- and macrovascular health of patients with T2DM.

Additionally, the recent long-term follow-up of the Steno-2 study²¹ showed that a multifactorial intervention striving for intensive glucose, BP, and lipid control that included the use of renin-angiotensin system blockers, aspirin, and lipid-lowering agents not only reduced the risk of nonfatal CVD among patients with T2DM and microalbuminuria, but also had sustained beneficial

effects on vascular complications and on rates of death from any cause and from CV causes. From a health care payer perspective, intensive multifactorial intervention was more likely to be cost-effective than conventional treatment in Denmark, especially if applied in a primary care setting.²²

Comprehensive care needed

The lower-than-expected rates of CV outcomes in the ACCORD, ADVANCE, VADT, and Steno-2 studies reinforce the importance of comprehensive diabetes care that treats not only hyperglycemia but also elevated BP and dyslipidemia; these are considered the “ABCs” of diabetes.^{11,19} The 2009 ADA standards of medical care guidelines recommend that for most T2DM patients, HbA1c should be maintained at less than 7.0%,³ while the American Association of Clinical Endocrinologists (AACE) 2007 guidelines state that HbA1c should be 6.5% or less.¹¹ Both organizations stress the importance of individualized goals, as discussed above, and advocate BP goals of less than 130/80 mm Hg and dyslipidemia goals of low-density lipoprotein cholesterol (LDL-C) less than 100 mg/dL, high-density lipoprotein cholesterol (HDL-C) greater than 40 mg/dL for men and 50 mg/dL for women, and triglycerides less than 150 mg/dL. It is recommended that an optional LDL-C goal of less than 70 mg/dL be considered for individuals with overt CVD.

CURRENT ANTIHYPERGLYCEMIC TREATMENT STRATEGIES

In response to new insights from clinical research and emerging treatment strategies, disease-specific organizations and medical specialty societies regularly revise and update their treatment guidelines and algorithms. These resources recommend that glycemic progress should be regularly monitored and pharmacologic therapy titrated or new drugs added promptly if glycemic goals are not met after 2 to 3 months.

Several algorithms combine scientific evidence with expert clinical opinion to guide physicians in treating their patients with T2DM. The American College of Endocrinology (ACE)/AACE road maps are designed to help develop individualized treatment regimens to achieve an HbA1c of 6.5% or less.²³ The algorithm from a writing group assembled by the ADA and the European Association for the Study of Diabetes (EASD) similarly promotes pharmacologic treatment together with lifestyle modifications to maintain a glycemic goal of HbA1c less than 7.0%.²⁴

OVERVIEW OF ANTIHYPERGLYCEMIC TREATMENT APPROACHES

Lifestyle measures, medical nutrition therapy, and appropriately prescribed physical activity are recommended for

virtually all patients with T2DM, as well as weight loss for those who are overweight or obese. Unfortunately, many patients cannot achieve glycemic goals with lifestyle measures alone and require the addition of pharmacotherapy.³ Extensive development of new therapies during the past 15 years has resulted in more than 11 classes of approved antihyperglycemic medications (Table 1) with diverse mechanisms of action and varied effects on HbA1c, body weight, lipids, and other factors.^{24–26}

Initial oral therapy

T2DM is usually treated initially with a single oral agent. Consistent with the progressive nature of the disease, patients often eventually require one or more additional oral agents and in many cases insulin.^{13,27} Choice of specific agents is based on individual patient circumstances, including the need for weight loss and control of fasting versus postprandial glucose, the presence of dyslipidemia and hypertension, and the risk for and potential consequences of hypoglycemia.²⁴ T2DM patients with severely uncontrolled and symptomatic hyperglycemia are best treated, at least initially, with a combination of insulin therapy and lifestyle intervention, often with metformin.

Metformin. The recently revised ADA/EASD writing group algorithm recommends that patients not requiring initial insulin begin treatment with metformin at the time of diagnosis unless there are contraindications.²⁴ Metformin is not associated with hypoglycemia and is considered weight-neutral, although some patients may lose weight.²⁸

Sulfonylureas. Sulfonylureas stimulate insulin secretion from pancreatic beta cells; their use may be associated with hypoglycemia and weight gain. Mechanisms for weight gain with sulfonylureas include reduction of glucosuria and increased caloric intake to prevent or treat hypoglycemia.^{11,28} Nateglinide and repaglinide are nonsulfonylurea oral insulin secretagogues. They result in rapid and relatively short-lived insulin responses and are usually administered three times a day, before each meal. Their use may be associated with weight gain and hypoglycemia.¹¹

Thiazolidinediones. Thiazolidinediones (TZD) increase insulin sensitivity in muscle, adipose tissue, and the liver. Hypoglycemia is uncommon with TZD monotherapy but weight gain related to increased and redistributed adiposity and fluid retention frequently occurs.

Alpha-glucosidase inhibitors. The alpha-glucosidase inhibitors are administered before meals and primarily reduce postprandial hyperglycemia. They are generally weight-neutral.²⁸

Insulin. Insulin and insulin analogues are the most effective antihyperglycemic agents, but their use can be associated with hypoglycemia and clinically significant weight gain.²⁸

TABLE 1**Currently available antihyperglycemic therapies for T2DM in the United States**

	Generic name(s)	Trade name(s)	Available as generic	Date of FDA approval
ORAL TREATMENTS, BY CLASS				
Sulfonylurea ^a	Glipizide	Glucotrol ^b	Yes	May 1984
	Glyburide	DiaBeta, Glynase, Micronase	Yes	May 1984
	Glimepiride	Amaryl	Yes	Nov 1995
Biguanide	Metformin hydrochloride	Glucophage ^c	Yes	Mar 1995
α -Glucosidase inhibitor	Acarbose	Precose	No	Sep 1995
	Miglitol	Glyset	No	Dec 1996
Thiazolidinedione (TZD)	Rosiglitazone	Avandia	No	Jun 1999
	Pioglitazone	Actos	No	Jul 1999
Meglitinide (glinide)	Repaglinide	Prandin	No	Dec 1997
	Nateglinide	Starlix	No	Dec 2000
DPP-4 inhibitor	Sitagliptin phosphate	Januvia	No	Oct 2006
	Saxagliptin	Onglyza	No	Jul 2009
Bile acid sequestrant	Colesevelam	Welchol	No	Jan 2008
Sulfonylurea and biguanide	Glyburide and metformin	Glucovance	Yes	Jul 2000
Biguanide and glitazone	Rosiglitazone maleate and metformin hydrochloride	Avandamet	No	Oct 2002
Sulfonylurea and glitazone	Rosiglitazone maleate and glimepiride	Avandaryl	No	Nov 2005
Biguanide and DPP-4 inhibitor	Sitagliptin and metformin hydrochloride	Janumet	No	Mar 2007
INJECTABLE TREATMENTS, BY CLASS				
Regular insulin	Human insulin (regular)	Humulin R, Novolin R	Yes	Oct 1982
Intermediate-acting insulin ^d	Human insulin (NPH insulin)	Humulin N, Novolin N	Yes	Oct 1982
Human insulin combinations	Insulin regular and NPH insulin	Humulin 70/30	Yes	Apr 1989
Rapid-acting insulin analogues	Insulin lispro	Humalog	No	Jun 1996
	Insulin aspart	Novolog	No	Jun 2000
	Insulin glulisine	Apidra	No	Apr 2004
Long-acting basal insulin analogues	Insulin glargine	Lantus	No	Apr 2000
	Insulin detemir	Levemir	No	Jun 2005
Combinations (including analogues) ^e	Insulin lispro protamine and insulin lispro	Humalog Mix 75/25 and 50/50	No	Dec 1999
	Insulin aspart protamine and insulin aspart	Novolog Mix 70/30	No	Nov 2001
Amylin analogue	Pramlintide acetate	Symlin	No	Mar 2005
GLP-1 receptor agonist	Exenatide	Byetta	No	Apr 2005

^a Other earlier-generation sulfonylureas (available as generic) include tolbutamide (Orinase), tolazamide (Tolinase), acetohexamide (Dymelor), and chlorpropamide (Diabinese).

^b Also available in extended-release formulation (Glucotrol XL).

^c Also available in extended-release formulation (Glucophage XR).

^d Other intermediate-acting insulins include Lente Humulin, Lente Iletin II, and Lente Novolin.

^e Premixed insulins include Humulin 70/30 and Novolin 70/30.

DPP-4 = dipeptidyl peptidase-4; FDA = US Food and Drug Administration; GLP-1 = glucagon-like peptide-1; NPH = insulin isophane (Neutral Protamine Hagedorn); T2DM = type 2 diabetes mellitus.

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Colesevelam. Colesevelam is a bile acid sequestrant that was recently approved by the US Food and Drug Administration as an antihyperglycemic therapy in people with T2DM. At a dosage of 1.875 g BID or 3.75 g QD in combination with a sulfonylurea, metformin, or insulin therapy, reductions in HbA1c compared with placebo in clinical trials of colesevelam have ranged from -0.5% to -0.7% ($P < .02$). Frequency of hypoglycemia and weight gain is low with this agent.²⁶

Weight management. Weight reduction is important for overweight or obese patients with T2DM.^{27,28} Even moderate weight loss (5% of body weight) can be associated with improved insulin action and reduced hyperglycemia.²⁹ Conversely, weight gain has been shown to worsen hyperglycemia and other CV risk factors. Treatment-related weight gain can also lead to decreased regimen adherence, contributing to poor glycemic control.²⁸

■ THE ROLE OF INCRETIN HORMONES AND INCRETIN-BASED THERAPIES IN T2DM PATIENTS

Over the last few years, the role of incretin hormones and their contribution to diabetes pathophysiology has become more apparent. The incretin effect refers to the observation that orally administered glucose elicits a greater insulin response than does glucose administered intravenously to produce equivalent blood glucose concentrations.^{30,31} The incretin effect is diminished in patients with T2DM.

Hormone mediation of the incretin effect

The two hormones that mediate the incretin effect are GIP (also known as gastric inhibitory polypeptide or glucose-dependent insulinotropic polypeptide) and glucagon-like peptide-1 (GLP-1).^{30,31} GLP-1 has several glucoregulatory actions, including enhancement of endogenous insulin release and suppression of inappropriate glucagon secretion, both in a glucose-dependent manner. Therefore, these effects of GLP-1 occur only when glucose concentrations are elevated, thereby minimizing the risk of hypoglycemia. GLP-1 also regulates gastric emptying; infusions of GLP-1 can slow the accelerated emptying that is often present in T2DM patients. GLP-1 also increases satiety and decreases food intake via a central mechanism.³¹

Because GLP-1 is rapidly inactivated by the enzyme dipeptidyl peptidase-4 (DPP-4), therapeutic use of GLP-1 would require continuous infusion, which is impractical.^{30,31} Two strategies have been used to produce incretin-related therapies. One, inhibition of the DPP-4 enzyme, results in a two- to threefold enhancement of endogenous GLP-1. The other, involving agents that resist breakdown by DPP-4 but bind to and activate the GLP-1 receptor, produces glucoregulatory effects similar to those of GLP-1.³⁰

Following subcutaneous (SC) injection, GLP-1 receptor agonists enhance insulin secretion and suppress inappropriately elevated glucagon, both in a glucose-dependent manner, as well as slow gastric emptying and enhance satiety.³⁰ DPP-4 inhibitors provide glucose-dependent enhanced insulin secretion and glucagon suppression, but they do not have the same effects on gastric emptying or satiety.

Clinically, the GLP-1 receptor agonists improve glycemia and are associated with weight loss.³²⁻³⁵ Adverse gastrointestinal symptoms are relatively common during the first few weeks of treatment. DPP-4 inhibitors improve glycemia but are weight-neutral and are not generally associated with significant gastrointestinal symptoms.^{32,36-38}

Incretin-based therapies

Incretin-based therapies are currently part of the antihyperglycemic armamentarium.^{25,32} The AACE guidelines¹¹ and the ACE/AACE roadmaps²³ include the GLP-1 receptor agonist exenatide and the DPP-4 inhibitor sitagliptin among antihyperglycemic therapies for patients with T2DM. The most recent update of the consensus algorithm statement of a joint ADA/EASD writing group included GLP-1 receptor agonists (but not DPP-4 inhibitors) in tier 2 of preferred agents, especially for patients who have concerns related to weight and hypoglycemia.²⁴ They noted that DPP-4 inhibitors may be appropriate choices in selected patients.

DPP-4 inhibitors: sitagliptin, saxagliptin. Until recently, sitagliptin was the only DPP-4 inhibitor available in the United States. Sitagliptin is approved by the FDA for treatment of T2DM at a recommended oral dosage of 100 mg QD, either as monotherapy or in combination with other oral antihyperglycemic medications. The dosage of sitagliptin should be reduced to 50 mg/day in patients with creatinine clearance (CrCl) levels that are between 30 mL/min and 50 mL/min and to 25 mg/day in those with CrCl less than 30 mL/min.³⁹

In a meta-analysis of incretin-based therapies, DPP-4 inhibitors produced a reduction in HbA1c compared with placebo (weighted mean difference of -0.74% ; 95% confidence interval, -0.85% to -0.62%).³² DPP-4 inhibitor antihyperglycemic efficacy has been shown to be similar whether used as a monotherapy or add-on therapy.^{32,37,38} This same meta-analysis showed DPP-4 inhibitors as having a neutral effect on weight.³² More recently, a single-pill combination of metformin and sitagliptin was approved.⁴⁰

A study comparing metformin, sitagliptin, and the combination of the two as initial monotherapy in T2DM patients with a baseline HbA1c of 8.8% showed 24-week HbA1c reductions from baseline of -0.66% with sitagliptin 100 mg QD, -0.82% with metformin 500 mg BID, and -1.90% with sitagliptin 50 mg + met-

formin 1,000 mg BID.⁴¹

On July 31, 2009, the FDA approved another DPP-4 inhibitor, saxagliptin, for the treatment of T2DM either as monotherapy or in combination with metformin, a sulfonylurea, or a TZD.⁴²

GLP-1 receptor agonist: exenatide. Exenatide, the only FDA-approved GLP-1 receptor agonist, is the synthetic version of exendin-4, which binds to the human GLP-1 receptor and in vitro possesses many of the glucoregulatory effects of endogenous GLP-1.^{30,32} Exenatide is indicated as monotherapy or adjunctive therapy for patients with T2DM who have not achieved adequate glycemic control with metformin, a sulfonylurea, a TZD, or metformin in combination with a sulfonylurea or a TZD.⁴³ Exenatide is administered by SC injection BID at a starting dosage of 5 µg BID for 4 weeks, followed by an increase to 10 µg BID.

Exenatide has been shown not only to enhance glucose-dependent insulin secretion but also to restore impaired first-phase insulin response in subjects with T2DM. Exenatide also helps control postprandial glycemic excursions by suppressing inappropriate glucagon secretion, slowing accelerated gastric emptying, and enhancing satiety. The increased satiety results in decreased food intake and weight loss.^{31,44} In a recent head-to-head crossover study, exenatide was shown to be more effective than sitagliptin in lowering postprandial glucose concentrations, increasing insulin secretion, and reducing postprandial glucagon secretion.⁴⁵ Exenatide also slowed gastric emptying and reduced caloric intake.

Exenatide, in most studies, resulted in a placebo-subtracted HbA1c reduction of approximately -1.0% and in one study lowered HbA1c from baseline by -1.5%. Completer analyses have shown HbA1c reductions of -1.0% up to 3 years and -0.8% up to 3.5 years. Exenatide has also been associated with a mean weight loss of as much as -3.6 kg at 30 weeks and as much as -5.3 kg at 3.5 years.^{33-35,46,47} A 1-year study showed that exenatide improved beta-cell secretory function compared with insulin glargine in metformin-treated patients with T2DM.⁴⁸ Long-term data, including findings from completed and intention-to-treat analyses of 82 weeks⁴⁹ to at least 3 years⁴⁷ have demonstrated that exenatide improved CV risk factors, including those related to BP, lipids, and hepatic injury biomarkers.

Therapies in development

Incretin-based therapies in development include a novel once-weekly formulation of exenatide; taspoglutide, another once-weekly GLP-1 receptor agonist; and liraglutide, a GLP-1 receptor agonist that is administered once daily.⁵⁰ Liraglutide is currently being evaluated in clinical trials as a once-daily SC injection.⁵¹⁻⁵³ Liraglutide has been reported to reduce HbA1c by -1.1%

at 26 weeks and up to -1.14% at 52 weeks and result in weight loss (up to -2.8 kg at 26 weeks and up to -2.5 kg at 52 weeks) in patients with T2DM who are treatment-naïve or taking other antidiabetes agents, including metformin, sulfonylurea, and TZD.⁵¹⁻⁵³ Evaluation of the once-weekly formulation of exenatide showed reductions in HbA1c of -1.9% at 30 weeks and -2.0% at 52 weeks with a weight loss of -3.7 kg at 30 weeks and -4.1 kg over 52 weeks of treatment.^{46,54}

CONCLUSION

In the United States, the epidemics of excessive weight and T2DM have contributed to an increased medical risk for many individuals. Comprehensive diabetes treatments targeting not only hyperglycemia but also frequently associated overweight/obesity, hypertension, and dyslipidemia will be required to reduce such risk. Current treatment strategies have evolved based on updated clinical guidelines and trials, as well as practice experience, including those related to newer agents. Incretin-based therapies, such as the GLP-1 receptor agonist, exenatide, and the DPP-4 inhibitors, sitagliptin and saxagliptin, are important additions to the treatment armamentarium, offering a reduction in hyperglycemia and beneficial effects on weight (reduction with exenatide and neutral with sitagliptin), and have been shown to improve several CV risk factors.

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Dr. Blonde reported that he wrote this article and received no assistance with content development from unnamed contributors. He reported that BlueSpark Healthcare Communications, a medical communications company, assisted with reference verification, proofing for grammar and style, table and figure rendering based on author instructions, copyright permission requests, and identification of topical overlap with other articles in this supplement.

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Role of the incretin pathway in the pathogenesis of type 2 diabetes mellitus

■ ABSTRACT

Nutrient intake stimulates the secretion of the gastrointestinal incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which exert glucose-dependent insulinotropic effects and assist pancreatic insulin and glucagon in maintaining glucose homeostasis. GLP-1 also suppresses glucose-dependent glucagon secretion, slows gastric emptying, increases satiety, and reduces food intake. An impaired incretin system, characterized by decreased responsiveness to GIP and markedly reduced GLP-1 concentration, occurs in individuals with type 2 diabetes mellitus (T2DM). The administration of GLP-1 improves glycemic control, but GLP-1 is rapidly degraded by the enzyme dipeptidyl peptidase-4 (DPP-4). Exenatide, a DPP-4-resistant exendin-4 GLP-1 receptor agonist, exhibits the glucoregulatory actions of GLP-1 and reduces body weight in patients with T2DM. It may possess cardiometabolic actions with the potential to improve the cardiovascular risk profile of patients with T2DM. DPP-4 inhibitors such as sitagliptin and saxagliptin increase endogenous GLP-1 concentration and demonstrate incretin-associated glucoregulatory actions in patients with T2DM. DPP-4 inhibitors are weight neutral. A growing understanding of the roles of incretin hormones in T2DM may further clarify the application of incretin-based treatment strategies.

■ KEY POINTS

The incretin effect may be responsible for up to 70% of insulin secretion following oral glucose ingestion; reduction of the incretin effect contributes to T2DM pathophysiology.

It is unknown whether incretin defects are a cause or consequence of T2DM.

Incretin therapies effectively lower glucose with concomitant favorable effects on body weight. GLP-1 receptor agonists reduce weight, while DPP-4 inhibitors are weight neutral.

It has long been understood that the pathophysiology of type 2 diabetes mellitus (T2DM) is based on the triad of progressive decline in insulin-producing pancreatic beta cells, an increase in insulin resistance, and increased hepatic glucose production.^{1,2} It is now evident that other factors, including defective actions of the gastrointestinal (GI) incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), also play significant roles.²⁻⁵ The uncontrolled hyperglycemia resulting from such defects may lead to microvascular complications, including retinopathy, neuropathy, microangiopathy, and nephropathy, and macrovascular complications, such as coronary artery disease and peripheral vascular disease.

This review explores the growing understanding of the role of the incretins in normal insulin secretion, as well as in the pathogenesis of T2DM, and examines the pathophysiologic basis for the benefits and therapeutic application of incretin-based therapies in T2DM.^{1,2}

■ THE GI SYSTEM AND GLUCOSE HOMEOSTASIS IN THE HEALTHY STATE

The GI system plays an integral role in glucose homeostasis.⁶ The observation that orally administered glucose provides a stronger insulinotropic stimulus than an intravenous glucose challenge provided insight into the regulation of plasma glucose by the GI system of healthy individuals.⁷ The incretin effect, as this is termed, may be responsible for 50% to 70% of the total insulin secreted following oral glucose intake.⁸

Two GI peptide hormones (the incretins)—GLP-1 and GIP—were found to exert major glucoregulatory actions.^{3,9,10} Within minutes of nutrient ingestion, GLP-1 is secreted from intestinal L cells in the distal ileum and colon, while GIP is released by intestinal K cells in the duodenum and jejunum.³ GLP-1 and GIP trigger their insulinotropic actions by binding beta-cell receptors.³ GLP-1 receptors are expressed on pancreatic glucagon-containing alpha and delta cells as well as on beta cells, whereas GIP receptors are expressed primarily on beta cells.^{3,8} GLP-1 receptors are also expressed in the central nervous system (CNS), peripheral nervous

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system, lung, heart, and GI tract, while GIP receptors are expressed in adipose tissue and the CNS.³ GLP-1 inhibits glucose-dependent glucagon secretion from alpha cells.³ In healthy individuals, fasting glucose is managed by tonic insulin/glucagon secretion, but excursions of postprandial glucose (PPG) are controlled by insulin and the incretin hormones.¹¹

Additionally, in animal studies, GLP-1 has been shown to induce the transcriptional activation of the insulin gene and insulin biosynthesis, thus increasing beta-cell proliferation and decreasing beta-cell apoptosis.¹² GLP-1 stimulates a CNS-mediated pathway of insulin secretion, slows gastric emptying, increases CNS-mediated satiety leading to reduced food intake, indirectly increases insulin sensitivity and nutrient uptake in skeletal muscle and adipose tissue, and exerts neuroprotective effects.⁸

Along with its insulinotropic action, GIP has been shown in animal studies to inhibit gastric acid secretion, bioregulate fat metabolism in adipocytes, increase glucagon secretion and fat deposition, increase beta-cell replication, and decrease beta-cell apoptosis.⁸ Figure 1 illustrates the biologic actions of GLP-1 and GIP.¹³

Both GLP-1 and GIP are rapidly degraded by the serine protease dipeptidyl peptidase-4 (DPP-4), which is widely expressed in bound and free forms.¹⁴ A recent study in healthy adults showed that GLP-1 concentration declined even during maximal DPP-4 inhibition, suggesting that there may be pathways of GLP-1 elimination other than DPP-4 enzymatic degradation.¹⁵

INCRETINS AND THE PATHOGENESIS OF T2DM

Studies have shown that incretin pathways play a role in the progression of T2DM.^{3,16} The significant reduction in the incretin effect seen in patients with T2DM has been attributed to several factors, including impaired secretion of GLP-1, accelerated metabolism of GLP-1 and GIP, and defective responsiveness to both hormones.¹⁶ Many patients with T2DM also have accelerated gastric emptying that may contribute to deterioration of their glycemic control.¹⁷

While GIP concentration is normal or modestly increased in patients with T2DM,^{16,18} the insulinotropic actions of GIP are significantly diminished.¹⁹ Thus, patients with T2DM have an impaired responsiveness to GIP with a possible link to GIP-receptor downregulation or desensitization.²⁰

Are secretory defects a cause or result of T2DM?

In contrast to GIP, the secretion of GLP-1 has been shown to be deficient in patients with T2DM.¹⁸ As with GIP, it is unknown to what degree this defect is a cause or consequence of T2DM. In a study of identical twins, defective GLP-1 secretion was observed only in the one sibling with T2DM, suggesting that GLP-1 secretory def-

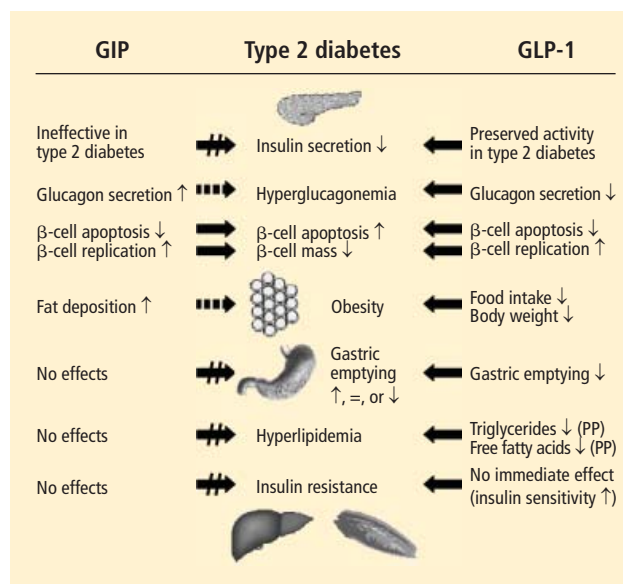


FIGURE 1. Biologic actions of GIP and GLP-1 in relation to the pathophysiology of type 2 diabetes mellitus. GIP = glucose-dependent insulinotropic polypeptide; GLP-1 = glucagon-like peptide-1; PP = postprandial; solid arrows = potentially beneficial actions; dashed arrows = potentially harmful actions; slashed arrows = actions with no effect.

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icits may be secondary to the development of T2DM.²¹ Despite the diminished secretion of GLP-1 in patients with T2DM, the insulinotropic actions of GLP-1 are preserved.¹⁹ It has also been shown that the effects of GLP-1 on gastric emptying and glucagon secretion are maintained in patients with T2DM.^{19,22,23}

Whether this incretin dysregulation is responsible for or is the end result of hyperglycemia remains a subject of continued investigation. A recent study confirmed that the incretin effect is reduced in patients with T2DM, but advanced the concept that it may be a consequence of the diabetic state.^{16,24} Notably, impaired actions of GLP-1 and GIP and diminished concentrations of GLP-1 may be partially restored by improved glycemic control.²⁴

Recent preclinical and clinical studies continue to clarify the roles of incretin hormones in T2DM. The findings from a study of obese diabetic mice suggest that the effect of GLP-1 therapy on the long-term remission of diabetes may be caused by improvements in beta-cell function and insulin sensitivity, as well as by a reduction in gluconeogenesis in the liver.²⁵

Incretin effect and glucose tolerance, body mass index

Another study was conducted to evaluate quantitatively the separate impacts of obesity and hyperglycemia on the incretin effect in patients with T2DM, patients

with impaired glucose tolerance, and patients with normal glucose tolerance.²⁶ There was a significant ($P \leq .05$) reduction in the incretin effect in terms of total insulin secretion, beta-cell glucose sensitivity, and the GLP-1 response to oral glucose in patients with T2DM compared with individuals whose glucose tolerance was normal or impaired. Each manifestation of the incretin effect was inversely related to both glucose tolerance and body mass index in an independent, additive manner ($P \leq .05$); thus, glucose tolerance and obesity attenuate the incretin effect on beta-cell function and GLP-1 response independently of each other.

Exogenous GLP-1 has been shown to restore the regulation of blood glucose to near-normal concentrations in patients with T2DM.²⁷ Several studies of patients with T2DM have shown that synthetic GLP-1 administration induces insulin secretion,^{19,27} slows gastric emptying (which is accelerated in patients with T2DM), and decreases inappropriately elevated glucagon secretion.^{19,23,28} Acute GLP-1 infusion studies showed that GLP-1 improved fasting plasma glucose (FPG) and PPG concentrations^{23,27}; long-term studies showed that this hormone exerts euglycemic effects, leading to improvements in glycosylated hemoglobin (HbA1c), and induces weight loss.²⁹

TARGETING FUNDAMENTAL DEFECTS OF T2DM WITH INCRETIN-BASED THERAPIES

Recognition and a better understanding of the role of the incretins and the enzyme involved in their degradation have led to the development of two incretin-based treatments: the GLP-1 receptor agonists, which possess many of the glucoregulatory actions of incretin peptides, and the DPP-4 inhibitors.⁵ Both the GLP-1 receptor agonists and the DPP-4 inhibitors have demonstrated safety and efficacy in the management of hyperglycemia in patients with T2DM.

GLP-1 receptor agonists

The GLP-1 receptor agonist exenatide is a synthetic form of exendin-4 and has a unique amino acid sequence that renders it resistant to degradation by DPP-4, making its actions longer lasting than endogenous GLP-1.^{5,30} Exenatide has a half-life of 2.4 hours and is detectable for up to 10 hours after subcutaneous (SC) injection.^{5,30} It is administered BID and has been approved as monotherapy or an adjunct therapy in patients with T2DM who have inadequate glycemic control following treatment with metformin, a sulfonylurea, a thiazolidinedione (TZD), or metformin in combination with a sulfonylurea or a TZD.^{31–35}

In both human and animal studies, exenatide has been shown to enhance glucose-dependent insulin secretion and suppress inappropriate glucagon secretion

in a glucose-dependent manner, reduce food intake and body weight, and acutely improve beta-cell function by enhancing first- and second-phase insulin secretion.^{5,36,37}

In a small study involving 17 patients with T2DM, exenatide was shown to slow gastric emptying, which could be an important mechanism contributing to its beneficial effects on PPG concentration.³⁸ Exenatide also has been shown to attenuate postprandial hyperglycemia, a risk factor for cardiovascular disease (CVD), by reducing endogenous glucose production by about 50% in patients with T2DM.³⁹ Another mechanism for glycemic control may exist, as a recent animal study has shown that exenatide, similar to endogenous GLP-1, lowers blood glucose concentration independent of changes in pancreatic islet hormone secretion or delayed gastric emptying.⁴⁰

A formulation of exenatide that is administered once weekly—exenatide long-acting release (LAR)—is in clinical evaluation and under review by the US Food and Drug Administration (FDA). In a short-term study, exenatide-LAR (0.8 mg or 2.0 mg) was administered once weekly for 15 weeks to patients with T2DM whose glycemia was suboptimally controlled with metformin alone or in combination with diet and exercise. Compared with placebo, treatment with exenatide once weekly was associated with markedly reduced HbA1c, FPG, PPG and body weight.⁴¹ In a larger, 30-week, phase 3 trial, Diabetes Therapy Utilization: Researching Changes in A1C, Weight and Other Factors Through Intervention with Exenatide ONce Weekly (DURATION-1), exenatide-LAR 2 mg once weekly was compared with exenatide 10 µg BID in patients with T2DM. Exenatide-LAR once weekly was associated with a significantly greater reduction in HbA1c (-1.9% vs -1.5% , $P = .0023$), and with a similar low risk of hypoglycemia and reduction in body weight (-3.7 kg vs -3.6 kg, $P = .89$) compared with the BID formulation.⁴²

Liraglutide, recently approved in the European Union for T2DM and also under regulatory review in the United States, is a DPP-4-resistant human analogue GLP-1 receptor agonist in clinical development that has a 97% homology to native GLP-1.^{43–45} In contrast to exenatide, the acetylated liraglutide molecule allows binding to serum albumin and provides resistance to DPP-4 degradation, thus prolonging the half-life of liraglutide to approximately 12 hours. Liraglutide is administered SC QD as monotherapy or in combination with other antidiabetes agents such as metformin or sulfonylurea to patients with T2DM.^{44–47} Liraglutide has been shown to reduce HbA1c, decrease body weight, and lead to a lower incidence of hypoglycemia compared with the sulfonylurea glimepiride.

DPP-4 inhibitors

Sitagliptin is a DPP-4 inhibitor indicated as monotherapy or in combination with metformin or a TZD

in patients with T2DM with inadequate glycemic control.^{48–51} Given orally, sitagliptin does not bind to the GLP-1 receptor agonist and has been shown to inhibit circulating DPP-4 activity by about 80%.^{52,53} Sitagliptin has been associated with an approximate twofold increase in postprandial GLP-1 plasma concentrations compared with placebo in healthy human subjects and in patients with T2DM.⁵³ Saxagliptin, another potent DPP-4 inhibitor, significantly reduced HbA1c and FPG concentrations in patients with T2DM⁵⁴ with a neutral effect on weight; it was recently approved by the FDA for treatment of T2DM.⁵⁵

The DPP-4 inhibitor vildagliptin is currently being used in the European Union and Latin America but has yet to receive regulatory approval in the United States.⁵⁴ Alogliptin, a novel, high-affinity, high-specificity DPP-4 inhibitor currently in development, provides rapid and sustained DPP-4 inhibition and significantly reduces HbA1c, FPG, and PPG concentrations with no change in body weight in patients with T2DM.^{56,57}

Incretin-based therapies compared

In a recent head-to-head crossover trial between the GLP-1 receptor agonist exenatide and the DPP-4 inhibitor sitagliptin, exenatide had a greater effect in reducing 2-hour PPG.⁵² Patients with T2DM who switched from sitagliptin to exenatide showed a further reduction in 2-hour PPG concentration. Exenatide was also more potent than sitagliptin in increasing insulin secretion, reducing postprandial glucagon secretion, and decreasing triglycerides.⁵² Finally, exenatide slowed gastric emptying and reduced caloric intake. The differences between the two incretin-based therapies and their effects on glycemic control could be attributed to the pharmacologic concentration of the GLP-1 receptor agonist exenatide that is available for GLP-1 receptor activation compared with the twofold rise in endogenous GLP-1 concentration seen with the DPP-4 inhibitor sitagliptin.⁵²

A comparison of the actions of the GLP-1 receptor agonists and DPP-4 inhibitors in patients with T2DM is provided in **Table 1**,^{52,58} and an overview of incretin-based therapies is presented in **Table 2**.^{45,54,59} GLP-1 receptor agonists induce weight loss in patients with T2DM, while DPP-4 inhibitors are weight neutral.^{3,52,58,60} The GLP-1 receptor agonists are associated with a much higher incidence of adverse GI effects such as nausea and vomiting, presumably also attributable to the pharmacologic levels achieved.

Effects of incretin-based therapies

The number of people with T2DM, overweight/obesity, or CVD, alone or in combination, is approaching epidemic proportions, with the mechanisms of these conditions interrelated. Approximately 24 million Americans

TABLE 1
Comparison of action of GLP-1 receptor agonists and DPP-4 inhibitors in patients with type 2 diabetes mellitus

Action	Injectable GLP-1 receptor agonists	Oral DPP-4 inhibitors
Insulin secretion	Enhanced ^a	Enhanced
Glucagon secretion	Suppressed ^a	Suppressed
Postprandial hyperglycemia	Reduced ^a	Reduced
Gastric emptying	Slowed significantly ^a	No effect
Appetite	Suppressed ^a	No effect
Satiety	Induced ^a	No effect
Body weight	Reduced	Neutral
β-cell function	Preservation; proinsulin/insulin ratio improved clinically	Preservation; proinsulin/insulin ratio improved clinically
Gastrointestinal adverse effects	Often	Rare to none

^aExenatide had a greater effect than sitagliptin on these parameters, based on a crossover study comparing exenatide and sitagliptin.⁵²

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1.

Adapted, with permission, from *Journal of Managed Care Pharmacy* (Triplitt C, et al. *J Manag Care Pharm* 2007; 13[suppl S-c]:S2–S16).⁵⁸ Copyright © 2007 Academy of Managed Care Pharmacy. All rights reserved.

have diabetes, and T2DM accounts for more than 90% of these cases.⁶¹ Most patients with T2DM are not achieving HbA1c targets.^{62–64} About 60% of deaths among patients with T2DM are caused by CVD.⁶⁵ Compounding the problem, overweight/obesity enhances the risk for CV-related morbidities in patients with diabetes.⁶⁶ A cluster of metabolic disorders referred to as the metabolic syndrome (which includes hyperglycemia, measures of central obesity, and a series of significant CV risk factors) is common in patients with T2DM and CVD.⁶⁷ Unfortunately, many antidiabetes drugs that successfully manage glycemic control also cause weight gain, which in theory may increase CV risk in patients with T2DM.⁶⁸

Data from studies of patients with T2DM show that exenatide improves glycemic control and reduces body weight. Exenatide administered BID significantly reduced HbA1c (–0.40% to –0.86%) and weight (–1.6 kg to –2.8 kg) relative to baseline in three 30-week, placebo-controlled clinical trials.^{31,33,34} In subsequent 2-year, open-label extension studies, exenatide produced significant reductions from baseline in HbA1c (–0.9% at 30 weeks) and weight (–2.1 kg at 30 weeks). Both decreases were sustained through 2 years (HbA1c –1.1%, weight –4.7 kg) with a low incidence of hypoglycemia.³¹ Further post

TABLE 2

Overview of incretin-based therapies

Drug	Approved indications	Average HbA1c lowering (%)	Route of administration	Dosing frequency	Weight effects
GLP-1 RECEPTOR AGONISTS					
Exenatide BID	Monotherapy or adjunct to metformin, a sulfonylurea, a TZD, a combination of metformin and a sulfonylurea, or a combination of metformin and a TZD to improve glycemic control in adults with T2DM	0.5–1.0	SC	BID	↓
Exenatide LAR	Investigational	1.8–1.9	SC	QW	↓
Liraglutide ^a	Investigational	0.5–1.6	SC	QD	↓
DPP-4 INHIBITORS					
Sitagliptin	Adjunct to diet and exercise to improve glycemic control in adults with T2DM	0.5–0.8	PO	QD	↔ ↑
Saxagliptin	Adjunct to diet and exercise to improve glycemic control in adults with T2DM	0.5–0.8	PO	QD	↔ ↑
Vildagliptin ^b	Investigational	0.5–0.8	PO	QD	↔ ↑
Alogliptin	Investigational	0.5–0.8	PO	QD	↔ ↑

^a Approved for use in patients with T2DM in the European Union.⁴⁵

^b Approved for use in patients with T2DM in parts of the European Union and Latin America.⁵⁴

BID = twice daily; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; HbA1c = glycosylated hemoglobin A1c; LAR = long-acting release; PO = orally; QD = once daily; QW = once weekly; SC = subcutaneous; T2DM = type 2 diabetes mellitus; TZD = thiazolidinedione

Adapted, with permission, from *The Journal of Family Practice* (www.jfponline.com).⁵⁹

hoc analysis of the open-label extension of the 30-week trials followed patients treated with exenatide BID for 3 years or longer.⁶⁹ In addition to markedly decreasing HbA1c from baseline levels (−1.1% at 3 years and −0.8% at up to 3.5 years; $P < .0001$), adjunctive exenatide produced significant reductions in body weight—up to −5.3 kg after 3.5 years of therapy.^{31,69} At 3.5 years, continued exenatide therapy resulted in a −6% reduction in low-density lipoprotein cholesterol, a 24% mean increase in high-density lipoprotein cholesterol, and a mean reduction in blood pressure of −2% to −4% from baseline levels. Improvements in hepatic biomarkers and homeostasis model assessment-B, a measure of beta-cell function, were seen after 2 and 3 years of exenatide treatment.³¹ Hypoglycemia was generally mild and transient.

In comparative head-to-head studies, exenatide BID and insulin analogues reduced HbA1c by similar magnitudes; yet exenatide treatment resulted in better control in terms of PPG and weight loss, while insulin glargine and insulin aspart produced weight gain.^{70–73}

Mechanisms of cardioprotective effects

Although the mechanisms for the potential cardioprotective effects of GLP-1 and its receptor agonists remain

to be fully elucidated, a recent study suggested that two novel pathways could be involved—one that is dependent on the known GLP-1 receptor pathway, and one that is independent of the GLP-1 receptor pathway.⁷⁴ Correlating with observations of a potential cardioprotective effect, an infusion of recombinant GLP-1 in patients with acute myocardial infarction, when added to standard therapy, resulted in improved left ventricular function and was associated with reduced mortality.⁷⁵ Evidence continues to accumulate for potential cardioprotective effects of the GLP-1 receptor agonists, indicating that they may have a positive impact on macrovascular complications in patients with T2DM.

CONCLUSION

T2DM, which is often associated with overweight and obesity, remains a significant challenge worldwide. The broad spectrum of glucoregulatory actions of the incretin hormones GLP-1 and GIP, and their importance in maintaining glucose homeostasis, have been recognized and correlated with the pathogenesis of T2DM. An improved understanding of the roles played by GLP-1 and GIP in the pathogenesis of T2DM may provide

clinicians with important details regarding the therapeutic application of incretin-based therapies, including the GLP-1 receptor agonist exenatide and the DPP-4 inhibitors sitagliptin and saxagliptin. Antidiabetes agents whose development is based on the multiple pharmacologic effects of incretin hormones can address the multifaceted nature of T2DM and overcome some current limitations of traditional therapies, especially those related to weight. This becomes more compelling given the close link among T2DM, obesity, and increased CV risk.

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Dr. Freeman reported that he wrote this article and received no assistance with content development from unnamed contributors. He reported that BlueSpark Healthcare Communications, a medical communications company, assisted with preliminary literature searches, reference verification, proofing for grammar and style, table and figure rendering based on author instructions, copyright permission requests, and identification of topical overlap with other manuscripts in this supplement.

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Patient and treatment perspectives: Revisiting the link between type 2 diabetes, weight gain, and cardiovascular risk

■ ABSTRACT

Lifestyle modifications in conjunction with antidiabetes medications can produce near-normal blood glucose concentrations in patients with type 2 diabetes mellitus (T2DM). Because these patients have increased cardiovascular morbidity and mortality, treatment strategies should also address the cardiovascular aspects of the disease, including blood pressure, lipids, and body weight. Since the prevalence of these abnormalities is increasingly secondary to poor diet and sedentary lifestyles and because most patients with T2DM are overweight/obese, clinicians are encouraged to help patients reduce body weight while correcting hyperglycemia by selecting treatment options that improve both parameters. The glucose-lowering properties of insulin and sulfonylureas are well known but they are also associated with weight gain. Thiazolidinediones are associated with weight gain as well as edema. However, this weight gain may be more peripheral than central, which may mitigate the risks associated with increased body fat. Metformin, the consensus first-line drug for the treatment of patients with T2DM, is weight neutral. Newer antidiabetes agents include incretin-based medications, such as the glucagon-like peptide-1 receptor agonists, which tend to decrease weight, and the dipeptidyl peptidase-4 inhibitors, which are weight neutral.

■ KEY POINTS

Control of cardiovascular risk factors is as important as glycemic control in patients with T2DM.

Intensive glucose control has shown mixed results in terms of correlation with improved cardiovascular risk factors.

Newer agents target the fundamental pathophysiologic defects of T2DM, with beneficial effects on weight and other cardiovascular risk factors.

Type 2 diabetes mellitus (T2DM), excess weight, and obesity are increasing in prevalence at alarming rates.¹⁻³ Concurrent with the increased prevalence is increased risk of morbidity and mortality. A healthy diet and exercise in conjunction with antidiabetes medications can help lower glucose concentration in patients with T2DM. Because these patients are at increased risk of cardiovascular (CV) morbidity and mortality, however, treatment strategies should address the CV risk factors, including blood pressure (BP), lipids, and body weight, as well as glycemic aspects of the disease.

To help clinicians manage the complex issues in treating patients with T2DM, this article presents an overview of patient and treatment perspectives relevant to overweight/obesity and CV disease (CVD). It includes an examination of the latest guidelines and algorithms for the management of T2DM, which continue to be updated and modified.

■ T2DM, WEIGHT GAIN OR OBESITY, AND CV RISK: A CHALLENGING TRIAD

Despite therapeutic advances in the diagnosis and treatment of diabetes and CVD over the last decade, the estimated number of persons in the United States older than 35 years with self-reported diabetes (with T2DM accounting for 90% to 95% of diagnosed cases) and CVD has increased from 4.2 million in 1997 to 5.7 million in 2005.^{3,4} The CV risk for patients with T2DM who have not had a CV event such as a myocardial infarction (MI) is similar to that of individuals without diabetes who have had a prior MI.⁵ Patients with T2DM have nearly double the mortality of those without the disease.⁶ Adding to their risk, about 80% of patients with T2DM are overweight or obese, conditions associated with worsened insulin resistance and increased CV risk and disease burden.^{7,8} Even a modest weight gain (5 kg) may increase the risk of coronary heart disease (CHD) by 30%, while associated changes in lipids and BP can increase the risk by another 20%.⁹

It is as important to control CV risk factors as it is

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to control glycemia in patients with T2DM, and both are difficult to achieve. Data from a recent nationwide Norwegian survey showed that only 13% of patients with T2DM achieved study-defined target levels; ie, glycosylated hemoglobin (HbA1c) less than 7.5%, BP less than 140/85 mm Hg, and total cholesterol/high-density lipoprotein (HDL-C) ratio less than 4.0.¹⁰

■ BENEFITS OF MANAGING GLYCEMIA, WEIGHT REDUCTION, AND CV RISK FACTORS

Several large studies, many ongoing, are generating data on the relationships among glycemia, weight reduction, and CV risk. It is well established that individuals with T2DM need aggressive risk factor reduction (glucose control, blood pressure management, and treatment of dyslipidemia) to optimize outcomes. However, characterization of the benefits of various components of risk factor reduction, particularly over many years, is only now occurring.

Results from the **United Kingdom Prospective Diabetes Studies (UKPDS)** showed the benefits and risks of pharmacologic glycemic control—essentially monotherapy with insulin or a sulfonylurea—compared with conventional dietary therapy in reducing diabetic complications in patients with newly diagnosed T2DM. In UKPDS 33, both insulin and sulfonylureas (intensive treatment) reduced the risk of microvascular end points (retinopathy, nephropathy) in patients whose median HbA1c was lowered to 7.0% at 10 years of follow-up, compared with patients who reached an HbA1c of 7.9%. However, intensive glycemic control did not translate into a statistically significant reduction in macrovascular complications, including MI, stroke, CVD, and death. Additionally, patients assigned to insulin had greater weight gain (+4.0 kg) than did patients assigned to receive the sulfonylurea chlorpropamide (+2.6 kg) or glyburide (+1.7 kg) ($P < .01$).¹¹

The UKPDS showed that intensive treatment with metformin reduced the risk of T2DM-related end points compared with conventional treatment (primarily diet alone) in overweight patients.¹² Although there were fewer patients in the metformin-treated subset ($n = 342$) than in the conventional treatment cohort, a secondary analysis showed that metformin was associated with less weight gain and fewer hypoglycemic episodes than either insulin or sulfonylurea therapy.¹² Since HbA1c levels in the treatment groups were equal, the additional benefits seen with metformin in overweight patients with T2DM were not based solely on glycemic control.

The **Action to Control Cardiovascular Risk in Diabetes (ACCORD)** trial involved 10,000 individuals with T2DM. The primary outcome measure was a composite of CV events. The intensively treated group was controlled to a target HbA1c of less than 6.0%,

with most patients receiving insulin. The trial was terminated early because an increased risk of sudden death was observed.¹³ A similar study, **Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE)**, evaluated more than 11,000 patients with T2DM, starting with a sulfonylurea-based regimen. In this study, there was no reduction in macrovascular events, but there was a reduction in nephropathy in the intensively treated group.¹⁴ In both studies, hypoglycemia and weight gain were more frequent in intensively treated patients; and in ACCORD, there were more episodes of severe hypoglycemia in the intensive-treatment group.^{13,14}

The **Veterans Affairs Diabetes Trial (VADT)** evaluated the effect of intensive glucose control on CVD in 1,791 patients (mean age, 60 years) with poorly controlled T2DM (average duration, 11.5 years). The primary end points included MI, stroke, new or worsening congestive heart failure (CHF), limb amputation, and invasive intervention for coronary or peripheral arterial disease. The hazard ratio for these end points in the intensive-treatment group was 0.88 (95% confidence interval [CI], 0.74 to 1.05).^{15,16} Specifically, the following beneficial effects were achieved:

- HbA1c reduced by -1.0% to -2.5% in absolute units,
- systolic BP (SBP) reduced by -4 to -7 mm Hg,
- diastolic BP (DBP) reduced by -7 to -8 mm Hg,
- low-density lipoprotein cholesterol (LDL-C) reduced by -27 to -28 mg/dL,
- triglycerides reduced by -44 to -50 mg/dL, and
- HDL-C increased by 4 to 5 mg/dL.

Despite these benefits, body weight increased approximately 9 to 18 lb (4 to 8 kg) during therapy.¹⁵

Since overweight and obesity are independent risk factors for CHD and CVD in patients with T2DM,¹⁷ weight management is an integral component in treatment. In the **Action for Health in Diabetes (Look AHEAD)** trial, an intensive exercise and weight-loss program resulted in clinically significant ($P < .001$) weight loss at 1 year in patients who had T2DM and a body mass index (BMI) greater than 25 kg/m² (> 27 kg/m² if receiving insulin).¹⁸ When compared with patients who received less structured, infrequent support and minimal education about diabetes, participants in the intensive program showed more weight loss, improved glucose control, decreased CV events, and reduced medicine use. The Look AHEAD trial is currently evaluating whether these improvements will continue to result in lower CV risk.

■ PATIENT ADHERENCE AND SATISFACTION

It is often challenging for patients with T2DM to adhere to their treatment regimens. The **Diabetes Attitude**,

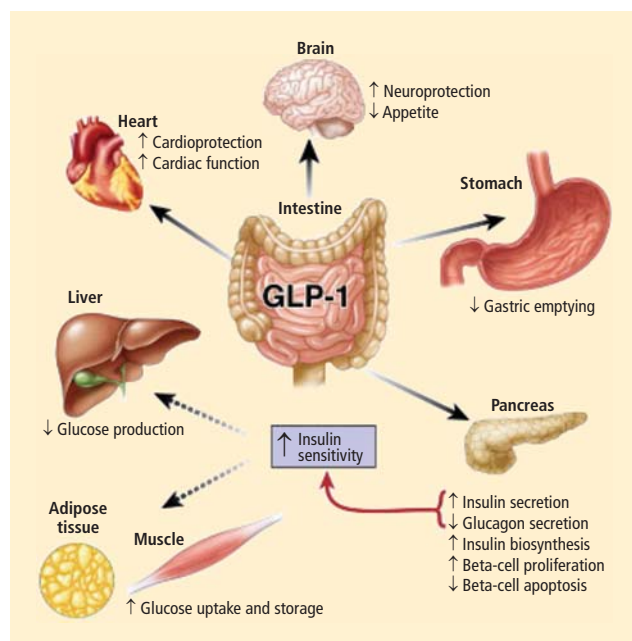


FIGURE 1. Actions of glucagon-like peptide-1 (GLP-1) in peripheral tissues. Most of the effects of GLP-1 are mediated by direct interaction with GLP-1 receptors on specific tissues. However, the actions of GLP-1 in liver, fat, and muscle most likely occur through indirect mechanisms.

Reprinted from *Gastroenterology* (Baggio LL, et al. Biology of incretins: GLP-1 and GIP. *Gastroenterology* 2007; 132:2131–2157).²⁹ Copyright © 2007, with permission from Elsevier. www.sciencedirect.com/science/journal/00165085.

Wishes, and Needs (DAWN) study examined psychosocial barriers to self-care in patients with diabetes and found that while 78% of patients with T2DM adhered to their medications, only 39% achieved complete success in at least two-thirds of their self-care domains.¹⁹ A multicenter, randomized, clinical trial examined the correlates of treatment satisfaction, including body weight, on patients' appraisal of treatment satisfaction with injectable insulin. The 14.5% of patients who experienced a reduction in BMI reported systematic improvement in treatment satisfaction.²⁰ Similarly, a cross-sectionally designed study (n = 99) that analyzed the interrelation of adherence, BMI, and depression in adults with T2DM found that patients with higher BMI and poor adherence also had depression, which was mediated by lower self-efficacy perceptions and increased diabetes symptoms.²¹ The results from these studies show a clear relationship between adherence with treatment regimens and achievement of HbA1c goals.²²

RECENT DEVELOPMENTS IN T2DM MANAGEMENT: STRATEGIES TO REDUCE CV RISK

Because excess weight and obesity are prominent features of T2DM, it is important to use an antidiabetes agent that does not induce unnecessary weight gain

(particularly central weight gain, which is thought to be most atherogenic).²³ Metformin, considered the first-line agent for treatment of T2DM, is generally weight neutral with a low level of hypoglycemia.^{24,25} Sulfonylureas, insulin, and thiazolidinediones (TZDs) are all associated with weight gain, although newer-analogue insulins may cause less weight gain than older agents. TZDs, especially pioglitazone, are associated with improvements in long-term beta-cell function and CV risk factors despite weight gain.^{26,27}

The newer antidiabetes agents belong to the dipeptidyl peptidase-4 (DPP-4) inhibitor and the glucagon-like peptide-1 (GLP-1) receptor agonist therapeutic classes and have been shown to be either weight neutral (DPP-4 inhibitors) or to cause weight loss (GLP-1 receptor agonists).²⁸

Figure 1 illustrates the physiologic role of GLP-1,²⁹ which induces glucose-dependent insulin secretion after food intake by binding to specific receptors on pancreatic beta cells, suppresses postprandial glucagon from pancreatic alpha cells, reduces postprandial plasma glucose (PPG) concentrations by delaying gastric emptying, and diminishes appetite.²⁸ The diminished secretion of GLP-1 in T2DM^{30,31} has led to the development of two different treatment approaches.²⁸ Since GLP-1 is rapidly degraded by DPP-4, GLP-1 receptor agonists have been developed to resist DPP-4 inactivation while exhibiting many of the actions of endogenous incretin hormones.^{28,29} DPP-4 inhibitors function as incretin enhancers by protecting endogenous GLP-1 and glucose-dependent insulinotropic peptide, another incretin, from enzymatic breakdown.^{31–33} Unlike the GLP-1 receptor agonists, which are administered subcutaneously (SC), DPP-4 inhibitors are administered orally.

Obesity and the incretin effect

A study in healthy subjects and patients with T2DM demonstrated that glucose tolerance and obesity independently impair the incretin effect, resulting in impaired insulin secretion and glucagon suppression.³⁴ Obesity is considered a subclinical inflammatory condition that releases chemokines, leading to insulin resistance. Figure 2 illustrates the interaction between obesity, inflammation, and insulin resistance.³⁵

Two recent studies showed that surgically induced weight loss enhances the physiologic “incretin effect.” In one study, obese individuals with T2DM whose weight loss was secondary to bariatric surgery combined with caloric restriction showed improved insulin sensitivity, improved carbohydrate metabolism, and elevated levels of adiponectin and GLP-1, all of which may reduce the incidence of T2DM.³⁶ In the other study, bariatric surgery in morbidly obese individuals with T2DM improved insulin secretion and ameliorated insulin resistance.³⁷

DPP-4 inhibitors

DPP-4 inhibitors such as sitagliptin and saxagliptin inhibit the enzymatic activity of DPP-4 and increase endogenous concentrations of GLP-1.²⁸ Sitagliptin has been compared with placebo as monotherapy and has been studied in combination with other therapies.

In an 18-week study, sitagliptin monotherapy, 100 and 200 mg QD, significantly reduced HbA1c compared with placebo (placebo-subtracted HbA1c reduction, -0.60% and -0.48% , respectively) in patients with T2DM. Sitagliptin also significantly decreased fasting plasma glucose (FPG) concentration relative to placebo.³⁸ Twelve weeks of sitagliptin monotherapy at dosages of 5, 12.5, 25, and 50 mg BID led to significant ($P < .001$) reductions in HbA1c compared with placebo. Sitagliptin also produced significant reductions in FPG and mean daily glucose concentrations across the doses studied.³⁹ Similar results were reported in other 12-week studies: 50 mg BID and 100 mg QD sitagliptin monotherapy significantly ($P < .05$) reduced HbA1c -0.39% to -0.56% and FPG concentration -11.0 to -17.2 mg/dL compared with placebo⁴⁰; sitagliptin 100 mg QD compared with placebo produced a least-squares mean change from baseline HbA1c of -0.65% versus 0.41% ($P < .001$) and FPG of -22.5 versus 9.4 mg/dL ($P < .001$).⁴¹

Sitagliptin also has been studied in combination with other therapies. After 24 weeks, sitagliptin combined with pioglitazone significantly reduced HbA1c by -0.70% and FPG by -17.7 mg/dL ($P < .001$ for both) compared with placebo.⁴² In another 24-week study, 100 mg sitagliptin QD significantly improved glycemic control and beta-cell function ($P < .05$ for both) in patients with T2DM who had inadequate glycemic control with glimepiride or glimepiride plus metformin.⁴³

In addition to significantly reducing HbA1c, sitagliptin 100 and 200 mg QD produced only small differences in body weight relative to placebo: least-squares mean change from baseline for sitagliptin 100 mg was -0.7 kg (95% CI, -1.3 to -0.1) and for 200 mg was -0.6 kg (95% CI, -1.0 to -0.2); for placebo it was -0.2 kg (95% CI, -0.7 to 0.2).³⁸ These findings were consistent with those from another 24-week monotherapy study where sitagliptin produced weight loss of up to -0.2 kg⁴⁴ and a 30-week study of sitagliptin added to ongoing metformin therapy. In the latter study, both sitagliptin and placebo resulted in weight reductions of -0.5 kg.⁴⁵

The effects of sitagliptin on lipids and BP have been reported in clinical studies in patients with and without T2DM. In one study of patients with T2DM, the addition of sitagliptin to metformin increased total cholesterol ($+8.1$ mg/dL), LDL-C ($+9.2$ mg/dL), and HDL-C ($+1.8$ mg/dL) but lowered triglyceride (-14.5 mg/dL) after 18 weeks of treatment (24-week data).⁴⁶ Data from a small ($n = 19$) study in nondiabetic patients with mild to moderate hypertension showed that sitagliptin pro-

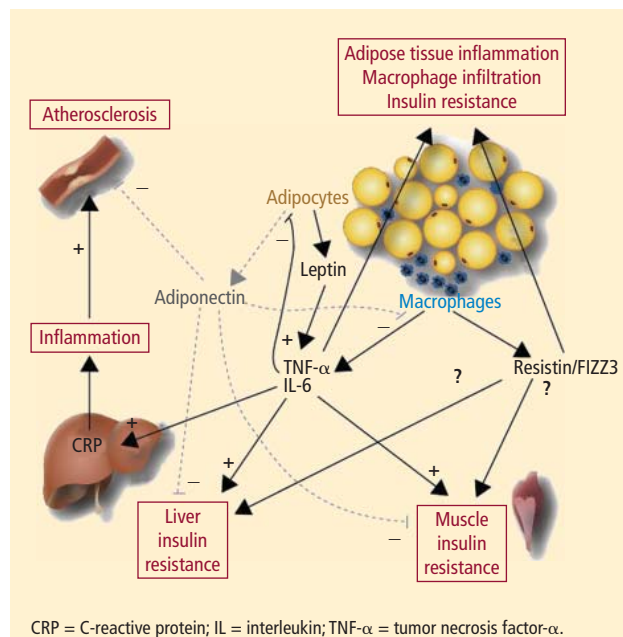


FIGURE 2. Adipokine expression and secretion by adipose tissue in insulin-resistant, obese subjects.

Reprinted from Bastard J-P, et al. Recent advances in the relationship between obesity, inflammation, and insulin resistance. *Eur Cytokine Netw* 2006; 17:4–12.³⁵ Copyright © 2006, with permission from Editions John Libbey Eurotext, Paris.

duced small reductions (-2 to -3 mm Hg) in 24-hour ambulatory BP measurements.⁴⁷

Another DPP-4 inhibitor, saxagliptin, with efficacy similar to that described for sitagliptin, was recently approved by the US Food and Drug Administration (FDA) for treatment of T2DM.⁴⁸

GLP-1 receptor agonists

Many of the GLP-1 receptor agonists developed or under development have glucoregulatory effects similar to GLP-1 but are resistant to degradation by DPP-4.²⁸ Exenatide, an exendin-4 receptor agonist, has compared favorably with sitagliptin and with insulin analogues. Long-acting (once-weekly and once-daily) GLP-1 receptor agonists are under development.

In a 2-week, head-to-head study in metformin-treated patients with T2DM, exenatide had a greater effect than sitagliptin in lowering PPG and was more potent in increasing insulin secretion and reducing postprandial glucagon secretion. In contrast to sitagliptin, exenatide slowed gastric emptying and reduced caloric intake.⁴⁹

In two studies of patients treated with exenatide, on a background of either metformin alone or metformin plus a sulfonylurea, patients who received metformin lost more weight (-1.6 to -2.8 kg; $P \leq .01$) and experienced more significant decreases from baseline HbA1c (-0.4% to -0.8% ; $P < .002$) at 30 weeks than did patients who received placebo.^{50,51} In a 16-week trial

of exenatide in patients previously treated with a TZD with or without metformin, exenatide reduced HbA1c -0.98% , fasting blood glucose -1.69 mmol/L, and body weight -1.51 kg.⁵²

When compared with insulin analogues, exenatide has been associated with weight loss (~ -3 kg) while the insulin analogues were associated with weight gain ($\sim +3$ kg).⁵³ After 26 weeks, body weight decreased -2.3 kg with exenatide and increased $+1.8$ kg with insulin glargine.⁵⁴ Similar results were found in a crossover non-inferiority trial, where the least-squares mean difference in weight change was significantly ($P < .001$) different (2.2 kg) between the treatments.⁵⁵ When exenatide was compared with insulin aspart in an open-label, noninferiority trial, there was a between-group difference in weight of -5.4 kg after 52 weeks.³²

Exenatide has also demonstrated these benefits in open-label extension studies. After 2 years, mean HbA1c reductions of -1.1% from baseline were sustained ($P < .05$), and weight loss of -4.7 kg was maintained ($P < .001$).⁵⁶ After 82 weeks, similar HbA1c decreases (-1.1%) and weight loss (-4.4 kg) were exhibited.⁵⁷ Even after 3 years, these benefits were maintained in patients who remained on the drug (HbA1c reduction from baseline, -1.0% ; weight loss, -5.3 kg [$P < .0001$ for both]).⁵⁸

Long-acting formulations of GLP-1 receptor agonists are in clinical development; two of these are once-weekly exenatide and once-daily liraglutide. Exenatide once weekly has the advantage of less frequent dosing and has elicited greater reductions in HbA1c than exenatide BID. After 15 weeks of once-weekly administration, the 0.8 -mg formulation reduced HbA1c -1.4% and the 2 -mg formulation reduced it -1.7% ($P < .0001$ for both compared with placebo). Body weight was lowered -3.8 kg ($P < .05$ compared with placebo) with the 2 -mg formulation.⁵⁹ Compared with exenatide BID, exenatide 2 mg once weekly showed greater reductions in HbA1c (-1.9% vs -1.5% ; $P = .0023$) after 30 weeks of therapy.⁶⁰ In a 1-year noncomparative trial, treatment with exenatide once weekly improved HbA1c (-2.0%) and weight (-4.1 kg), as well as BP and lipid profiles compared with baseline.⁶¹

Liraglutide, a once-daily human analogue GLP-1 receptor agonist, is under review by the FDA.²⁸ In a 26-week study of patients with T2DM, liraglutide was associated with reductions in HbA1c (mean, -1.04% ; $P = 0.067$ compared with insulin) and body weight (mean, -2.5 kg; $P < .001$ compared with insulin) at dosages of 0.6 to 1.8 mg/day SC. Liraglutide produced a decline in SBP from 0.6 to 3 mm Hg but was not associated with a decrease in DBP.⁶² In a 52-week study comparing liraglutide with glimepiride monotherapy, liraglutide 1.2 mg was associated with an HbA1c reduction of -0.84% ($P = .0014$) and the 1.8 -mg dose with a reduction of -1.14%

($P < .0001$) compared with -0.51% for glimepiride. SBP decreased -0.7 mm Hg with glimepiride compared with -2.1 mm Hg for liraglutide 1.2 mg ($P = .2912$) and -3.6 mm Hg for liraglutide 1.8 mg ($P < .0118$). Mean DBP fell slightly but not significantly in all treatment groups.⁶³ No effects on lipid parameters were reported in these two liraglutide studies.

The **Liraglutide Effect and Action in Diabetes (LEAD-6)** trial was undertaken to compare exenatide (10 μ g BID SC) and liraglutide (1.8 mg/day SC) as add-on therapy to metformin, a sulfonylurea, or a combination of both in 464 patients with T2DM. After 26 weeks of treatment, liraglutide was associated with a significant reduction in HbA1c of -1.12% , compared with -0.79% with exenatide ($P < .0001$). Patients treated with liraglutide lost -3.2 kg while those on exenatide lost -2.9 kg. Among patients previously treated with metformin alone, there was a 1 -kg difference in favor of liraglutide ($P = \text{NS}$).⁶⁴

Safety profile

All of the drugs discussed have potential adverse effects. Metformin continues to have a black box warning for lactic acidosis.⁶⁵ Sulfonylureas and insulin can cause hypoglycemia. TZDs can cause fluid retention and, in rare cases, CHF (for which these drugs also carry a black box warning).^{66,67} TZDs also increase the risk of distal fracture.^{66,67} The most common side effects of exenatide are gastrointestinal, but there have been reported cases of pancreatitis, some of which have been fatal.^{68,69} It has been difficult to prove whether exenatide increases the risk of pancreatitis, as patients with T2DM are already at an increased (three- to fourfold) risk for this condition compared with persons who do not have T2DM.⁶⁹ Exenatide should not be used in patients with severe renal impairment or end-stage renal disease; it should be used with caution in patients who have undergone renal transplantation and in patients with moderate renal impairment.

The prescribing information for sitagliptin includes pancreatitis among the adverse reactions identified during the drug's postapproval use.⁷⁰ As with exenatide, it is not fully known whether a true association exists between the agent and pancreatitis. However, since pancreatitis can occur in this patient population, it is recommended that abdominal pain be fully evaluated to rule out pancreatitis. Continued postmarketing surveillance is important for all of these agents.

THE ROLE OF GUIDELINES

The American Association of Clinical Endocrinologists (AACE),²⁶ the American Diabetes Association (ADA),⁷¹ and the ADA in conjunction with the European Association for the Study of Diabetes (EASD)²⁴ have recently revised their recommendations for the

management of patients with diabetes. The guidelines are unanimous in setting a glycemic goal ($\text{HbA1c} < 7.0\%$ for the ADA, $\text{HbA1c} \leq 6.5\%$ for the AACE) and advocating individualized care for a treatment goal of HbA1c lower than 6.0% in patients who stand to benefit from near euglycemia without inducing severe hypoglycemia.^{24,26,71}

CVD is the major cause of morbidity and mortality associated with T2DM and is a source of increasing concern.⁵ Accordingly, special consideration should be given to patients with coexisting CV risk factors, including hypertension and dyslipidemia. The ADA and the EASD advocate lifestyle modification to decrease body weight and the concurrent initiation of metformin as first-line therapy.²⁴ If that strategy is insufficient, then two tiers of treatment guide the choice of next steps²⁴:

- Tier 1, in addition to metformin, includes the sulfonylureas and insulin. Although these are excellent glucose-lowering drugs, they are associated with weight gain, hypoglycemia, and no improvement in BP or lipid levels. They are relatively low in cost and have been used for many years. Their main drawback is evidence that despite their use, beta-cell failure continues unabated over time.

- Tier 2 treatments include pioglitazone and the GLP-1 receptor agonist exenatide. Consideration may be given to the use of pioglitazone or exenatide when hypoglycemia is of concern, with exenatide being preferred when weight loss is a major objective and HbA1c is close to target ($< 8.0\%$).²⁴ Additionally, both the TZDs and exenatide probably help slow the rate of beta-cell failure, particularly if they are used early in the course of the disease.^{72,73} The AACE recommends different pharmacologic approaches based on HbA1c at diagnosis.²⁶

The American Heart Association and the ADA have issued a joint scientific statement on the primary prevention of CVD in patients with diabetes.⁷⁴ They advocate lifestyle management of body weight, nutrition, and physical activity.⁷⁴ In addition, they stress the need for attention to BP, lipid levels, and smoking status, and the use of antiplatelet agents in patients at increased CV risk (> 40 years of age and a family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria).

CONCLUSION

T2DM, weight gain/obesity, and CV risk present a continuing challenge to patients and clinicians. Anti-diabetes agents have varying degrees of evidence to support their effects on HbA1c , body weight, BP, and lipid levels. A better understanding of the pathophysiology of T2DM has led to the development of newer antidiabetes agents that target the fundamental defects of the disease. Evidence continues to accumulate for the improved benefits of glycemic control and weight loss in

T2DM with GLP-1 receptor agonists such as exenatide currently having robust data in terms of beneficial effects on weight and CV risk factors. As clinicians continue to incorporate this knowledge into their practice patterns, patient adherence and clinical outcomes are expected to improve. Newer agents, such as incretin-based therapies, address T2DM as well as other factors that increase cardiometabolic risk through their effects not only on glycemic control but on body weight, BP, and lipids.

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Dr. Peters reported that she wrote this article and received no assistance with content development from unnamed contributors. She reported that BlueSpark Healthcare Communications, a medical communications company, assisted with preliminary literature searches, reference verification, proofing for grammar and style, table and figure rendering based on author instructions, copyright permission requests, and identification of topical overlap with other manuscripts in this supplement.

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Advances in therapy for type 2 diabetes: GLP-1 receptor agonists and DPP-4 inhibitors

■ ABSTRACT

Type 2 diabetes mellitus (T2DM) is intrinsically connected to overweight and obesity. It is a complex metabolic disorder that predisposes patients to, and is associated with, cardiovascular disease. In addition to the triumvirate of core defects associated with T2DM (involvement of the pancreatic beta cell, the muscle, and the liver), other mechanisms including hyperglucagonemia, accelerated gastric emptying, and incretin deficiency/resistance are also involved. This has led to the development of incretin-based therapies, such as glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors. These newer therapies have beneficial effects on glycosylated hemoglobin A1c (HbA1c) levels, weight, and pancreatic beta-cell function.

■ KEY POINTS

Hormonal deficiencies in T2DM are related to abnormalities in the secretion of amylin, glucagon, and incretin hormones.

In clinical trials, GLP-1 receptor agonists reduced HbA1c levels, had beneficial effects on weight, and caused less hypoglycemia than insulin analogues.

Both GLP-1 receptor agonists and DPP-4 inhibitors improve pancreatic beta-cell function.

Incretin-based therapies have been incorporated into recently updated clinical guidelines for treatment of T2DM.

The prevalence of type 2 diabetes mellitus (T2DM) is increasing exponentially worldwide. According to the Centers for Disease Control and Prevention, more than 23 million Americans had diabetes in 2007.¹ Globally, the prevalence of diabetes, of which T2DM accounts for 90% to 95% of cases,¹ is expected to increase from 171 million in 2000 to 366 million in 2030.² The National Health and Nutrition Examination Survey (NHANES) showed that about 66% of Americans were overweight or obese between 2003–2004.³ Data from a Swedish National Diabetes Register study showed both overweight and obesity as independent risk factors for cardiovascular disease (CVD) in patients with T2DM.⁴

This article presents an overview of the evolving concepts of the pathophysiology of T2DM, with a focus on two new therapeutic classes: the glucagon-like peptide-1 (GLP-1) receptor agonists and the dipeptidyl peptidase-4 (DPP-4) inhibitors.

■ THE PATHOPHYSIOLOGY OF T2DM

The American Association of Clinical Endocrinologists (AACE) describes T2DM as “a progressive, complex metabolic disorder characterized by coexisting defects of multiple organ sites including insulin resistance in muscle and adipose tissue, a progressive decline in pancreatic insulin secretion, unrestrained hepatic glucose production, and other hormonal deficiencies.”⁵ Other defects include accelerated gastric emptying in patients with T2DM, especially those who are obese or who have the disease for a long duration.^{6,7}

Hormonal deficiencies in T2DM are related to abnormalities in the secretion of the beta-cell hormone amylin, the alpha-cell hormone glucagon, and the incretin hormones GLP-1 and glucose-dependent insulinotropic polypeptide (GIP).^{8,9} In addition to the triumvirate of core defects associated with T2DM (involvement of the pancreatic beta cell, muscle, and liver), other mechanisms of disease onset have been advanced, including accelerated lipolysis, hyperglucagonemia, and incretin deficiency/resistance.⁹ Also, the rate of basal hepatic glucose production is markedly increased in patients with T2DM, which is closely

correlated with elevations in fasting plasma glucagon concentration.⁹

The incretin effect—the intestinal augmentation of secretion of insulin—attributed to GLP-1 and GIP is reduced in patients with T2DM.¹⁰ The secretion of GIP may be normal or elevated in patients with T2DM while the secretion of GLP-1 is deficient; however, cellular responsiveness to GLP-1 is preserved while responsiveness to GIP is diminished.¹¹

Both endogenous and exogenous GLP-1 and GIP are degraded in vivo and in vitro by the enzyme DPP-4,¹² a ubiquitous, membrane-spanning, cell-surface aminopeptidase that preferentially cleaves peptides with a proline or alanine residue in the second amino-terminal position. DPP-4 is widely expressed (eg, in the liver, lungs, kidney, lymphocytes, epithelial cells, endothelial cells). The role of DPP-4 in the immune system stems from its exopeptidase activity and its interactions with various molecules, including cytokines and chemokines.¹³

■ INCRETIN-BASED THERAPIES: GLP-1 RECEPTOR AGONISTS AND DPP-4 INHIBITORS

Exenatide is a GLP-1 receptor agonist that is resistant to DPP-4 degradation. Based on preclinical studies, exenatide, which shares a 53% amino acid sequence identity with human GLP-1, is approximately 5,500 times more potent than endogenous GLP-1 in glucose lowering.^{14,15} Among the acute actions of exenatide is glucose-dependent insulinotropism, the end result of which may be a reduced risk of hypoglycemia.¹⁶ This contrasts with insulin secretagogues (eg, sulfonylureas), which increase insulin secretion regardless of glucose concentrations.

Exenatide received US Food and Drug Administration (FDA) approval in 2005 and is indicated for the treatment of patients with T2DM.^{13,17} Exenatide is administered BID as a subcutaneous (SC) injection in doses of 5 or 10 µg within 1 hour before the two major meals of the day, which should be eaten about 6 hours apart.¹⁸

Approved in 2006, sitagliptin was the first DPP-4 inhibitor indicated for adjunctive therapy to lifestyle modifications for the treatment of patients with T2DM.¹⁷ The recommended dosage of oral sitagliptin is 100 mg QD. A single-tablet formulation of the combination of sitagliptin and metformin was approved by the FDA in 2007.¹⁹ Another DPP-4 inhibitor, saxagliptin, was approved in July 2009 for treatment of patients with T2DM either as monotherapy or in combination with metformin, sulfonylurea, or a thiazolidinedione (TZD).²⁰ The DPP-4 inhibitor vildagliptin is approved in the European Union and Latin America but not in the United States. Vildagliptin is available as a 50-

100-mg daily dosage; it has been recommended for use at 50 mg QD in combination with a sulfonylurea or at 50 mg BID with either metformin or a TZD.¹⁸

■ GLP-1 RECEPTOR AGONISTS AND DPP-4 INHIBITORS IN DEVELOPMENT

Exenatide is currently being evaluated as a once-weekly formulation.^{21,22} Compared with the BID formulation, exenatide once weekly has been shown to produce significantly greater improvements in glycemic control, with similar reductions in body weight and no increased risk of hypoglycemia.²¹

Also undergoing regulatory review is the partly DPP-4-resistant acylated GLP-1 receptor agonist liraglutide.¹³ Liraglutide, a human analogue GLP-1 receptor agonist, has 97% linear amino acid sequence homology to human GLP-1.^{23,24} Based on its prolonged degradation time and resulting 10- to 14-hour half-life, liraglutide is anticipated to be dosed once daily.^{13,25,26}

Other GLP-1 receptor agonists and DPP-4 inhibitors are in varying stages of development.²⁷ Albiglutide is a long-acting GLP-1 receptor agonist that is generated by the genetic fusion of a DPP-4-resistant GLP-1 to human albumin. Based on pharmacokinetic studies, albiglutide has a half-life of 6 to 8 days. AVE0010, an exendin-4-based GLP-1 receptor agonist, was shown in a 28-day T2DM clinical trial to have an affinity four times greater than native GLP-1 for the human GLP-1 receptor.²⁷ Taspoglutide (R1583), a human analogue GLP-1 receptor agonist, was evaluated in three randomized, placebo-controlled studies as a GLP-1 receptor agonist. Alogliptin, a DPP-4 inhibitor currently in development, has been shown to be safe and effective in studies as monotherapy and in combination with other antidiabetes agents.^{28–30}

■ CLINICAL TRIALS: GLP-1 RECEPTOR AGONISTS AND DPP-4 INHIBITORS

This section summarizes clinical trials of GLP-1 receptor agonists and DPP-4 inhibitors. The summary is based on literature published from 2005 to 2009 relevant to phase 3 or 4 T2DM clinical trials with currently available agents, or agents with pending new drug applications.

Table 1 summarizes the data on the effects of the GLP-1 receptor agonists on glucose lowering based on glycosylated hemoglobin (HbA1c) mean changes from baseline, body weight, and hypoglycemia. Eleven studies were identified for exenatide, including three pivotal trials,^{31–33} three insulin-comparator studies,^{34–36} one long-term study,³⁷ one monotherapy study (a use for which it is not currently indicated),³⁸ one head-to-head study with a DPP-4 inhibitor,³⁹ and two studies with exenatide once weekly (which is currently investiga-

TABLE 1**Effects of the GLP-1 receptor agonists on HbA1c, weight, and hypoglycemia in patients with T2DM**

Study	Study population/ duration of therapy	Study agents	HbA1c (mean ΔBL)	Weight (mean ΔBL)	Hypoglycemia
EXENATIDE					
DeFronzo 2005 ³¹	Pivotal study in patients receiving MET N = 272/30 wk	E: 5 or 10 µg BID SC PL	E: -0.40% to -0.78% PL: +0.8% (<i>P</i> < .002)	E: -1.6 kg to -2.8 kg PL: -0.3 kg (<i>P</i> < .001)	E vs PL: 5% vs 5%
Kendall 2005 ³²	Pivotal study in patients receiving MET and an SU N = 733/30 wk	E: 5 or 10 µg BID SC PL	E: -0.6% to -0.8% PL: +0.2% (<i>P</i> < .0001)	E: -1.6 kg PL: -0.9 kg (<i>P</i> ≤ .01)	E vs PL: 23% vs 13%
Zinman 2007 ³³	Pivotal study in patients receiving a TZD ± MET N = 233/16 wk	E: 10 µg BID SC PL	E: -0.89% PL: +0.09% (<i>P</i> < .001)	E: -1.75 kg PL: -0.24 kg (<i>P</i> < .001)	E vs PL: 11% vs 7%
Barnett 2007 ³⁴	IN-comparator noninferiority study N = 138/2 16-wk trial periods	E: 10 µg BID SC IN GL: QD titrated to FSG ≤ 5.6 mmol/L	E: -1.36% IN GL: -1.36% (<i>P</i> < .001)	E: -2.0 kg to -2.2 kg IN GL: +1.0 kg to +2.3 kg	E vs IN GL: 15% vs 25%
Heine 2005 ³⁵	IN-comparator study in patients with HbA1c 7.0%-10.0% despite MET and SU N = 551/26 wk	E: 10 µg BID SC IN GL: QD titrated to FBG < 5.6 mmol/L (100 mg/dL)	E: -1.11% IN GL: -1.11%	E: -2.3 kg IN GL: +1.8 kg	E vs IN GL: 7.3 vs 6.3 events/patient-yr
Nauck 2007 ³⁶	IN-comparator study N = 501/52 wk, while continuing with MET and SU	E: 5 µg BID SC for 4 wk, 10 µg thereafter Biphasic IN AS BID SC, titrated to optimal control	E: -1.04% IN AS: -0.89%	E: -2.5 kg IN AS: +2.9 kg (<i>P</i> < .001)	E vs IN AS: 17% vs 25%
Klonoff 2008 ³⁷	Long-term open-label study to assess glycemic control, CV risk, and hepatic injury markers N = 217 completed 3 yr of therapy, N = 151 completed 3.5 yr of therapy	E: 5 or 10 µg BID SC for 30 wk, then 5 µg BID SC for 4 wk, then 10 µg BID SC for ≥ 3 yr	At 3 yr: E: -1.0% (<i>P</i> < .0001) At 3.5 yr: E: -0.8% (<i>P</i> < .0001)	At 3 yr: E: -5.3 kg (<i>P</i> < .0001) At 3.5 yr: E: -5.3 kg (<i>P</i> < .0001)	Hypoglycemia with E, usually mild to moderate: 40%
Moretto 2008 ³⁸	Monotherapy study N = 232/24 wk	E: 5 or 10 µg BID SC PL	E: -0.7% to -0.9% PL: -0.2%	E: -2.8 kg to -3.1 kg PL: -1.4 kg	E vs PL: 4% vs 1%
DeFronzo 2008 ³⁹	First clinical head-to-head study between a GLP-1 receptor agonist and a DPP-4 inhibitor, in patients receiving MET N = 61/crossover study with two treatment periods of 2 wk preceded by 1-wk PL lead-in and no interval washout	E: 5 µg BID SC for 1 wk, then 10 µg BID SC for 1 wk ST: 100 mg QD PO for 2 wk	E: -15 mg/dL (FPG) ST: -19 mg/dL (FPG) (<i>P</i> = .3234)	E: -0.8 kg ST: -0.3 kg (<i>P</i> = .0056)	No major hypoglycemic events with E or ST

Table continues on next page

tional).^{21,22} Five primary efficacy studies with liraglutide were also identified.^{23,25,26,40,41}

Table 2 summarizes the corresponding data for the DPP-4 inhibitors. Ten studies with sitagliptin were identified, including four monotherapy studies,⁴²⁻⁴⁵ one head-to-head study with a GLP-1 receptor agonist,³⁹ and five studies in which sitagliptin was used in combination or as add-on therapy.⁴⁶⁻⁵⁰ Five saxagliptin studies are reviewed, including two in which saxagliptin was used in combination with metformin and one in combination with glyburide.⁵¹⁻⁵⁵ Six studies with vildagliptin were reviewed,⁵⁶⁻⁶¹ but no trials specific to the single-tablet formulation of sitagliptin plus metformin were identified.

Effects on HbA1c and weight

GLP-1 receptor agonists reduced HbA1c. Based on the studies reviewed in **Table 1**, exenatide BID reduced baseline HbA1c by a maximum of -1.5% at 30 weeks.^{21,31,32} Exenatide has demonstrated sustained reductions in HbA1c of -0.8% for up to 3.5 years in an open-label extension trial.³⁷ Even greater reductions in HbA1c (-1.4% at 15 weeks and -1.9% at 30 weeks) have been reported with the once-weekly formulation under clinical development.^{21,22} Liraglutide, another GLP-1 receptor agonist under development, has reported HbA1c reductions from baseline up to -1.67% at 14 weeks,^{40,41} up to -1.1% at 26 weeks,^{23,26} and up to -1.14% at 52 weeks.²⁵ The reductions quoted generally

TABLE 1 (continued)**Effects of the GLP-1 receptor agonists on HbA1c, weight, and hypoglycemia in patients with T2DM**

Study	Study population/ duration of therapy	Study agents	HbA1c (mean Δ BL)	Weight (mean Δ BL)	Hypoglycemia
Kim 2007 ²²	Pilot study of E once weekly ^a N = 45/15 wk	E: 0.8 or 2.0 mg QW SC PL	E QW: -1.4% to -1.7% PL: $+0.4\%$ ($P < .0001$)	E QW: -3.8 kg PL: 0 kg ($P < .05$)	E QW vs PL: 25% vs 0%
Drucker 2008 ²¹	DURATION-1 study: E QW ^a vs E BID N = 295/30 wk	E: 2 mg QW SC E: 10 μ g BID SC	E QW: -1.9% E BID: -1.5% ($P = .023$)	E QW: -3.7 kg E BID: -3.6 kg ($P = .89$)	No major hypoglycemic events with E QW or E BID
LIRAGLUTIDE^a					
Vilsbøll 2007 ⁴¹	Placebo-controlled study N = 165/14 wk	L: 0.65, 1.25, or 1.90 mg QD SC PL	L: -0.98% to -1.45% PL: $+0.29\%$ ($P < .0001$)	L: -2.99 kg PL: -1.78 kg ($P = .390$ for L 1.90 mg)	No major or minor hypoglycemic events with L or PL
Seino 2008 ⁴⁰	Dose-response study in Japanese patients treated with diet \pm oral agents N = 226/14 wk	L: 0.1, 0.3, 0.6, or 0.9 mg QD SC PL	L: -0.72% to -1.67% PL: $+0.09\%$	L: -0.48 kg to $+0.13$ kg PL: -0.95 kg	No major or minor hypoglycemic events with L or PL
Nauck 2009 ²⁶	LEAD-2 study N = 1,091/26 wk, in combination with MET and in patients previously treated with oral agents	L: 0.6, 1.2, or 1.8 mg/d QD SC G: 4 mg QD PO PL	L: -0.7% to -1.0% G: -1.0% PL: $+0.1\%$	L: -1.8 kg to -2.8 kg G: $+1.0$ kg PL: -1.5 kg ($P < .0001$ vs G; $P \leq .01$ vs PL)	No major hypoglycemic events with L, G, or PL
Garber 2009 ²⁵	LEAD-3-Mono N = 746/52 wk, as monotherapy	L: 1.2 or 1.8 mg QD SC G: 8 mg QD PO	L: -0.84% to -1.14% G: -0.51% ($P < .001$)	L: -2.0 kg to -2.5 kg G: $+1.0$ kg	No major hypoglycemic events with L or G
Marre 2009 ²³	LEAD-1 SU N = 1,041/26 wk, added to SU (G) 2–4 mg/d	L: 0.6, 1.2, or 1.8 mg QD SC + R PL R = L PL + R 4 mg/d PL = L PL + R PL	L: 1.2 mg or 1.8 mg: -1.1% ($P < .0001$) R: -0.4% ($P < .0001$) PL: $+0.2\%$	L: 1.2 mg or 1.8 mg: -0.2 kg to $+0.7$ kg R: $+2.1$ kg PL: $+0.1$ kg	Minor hypoglycemia: $< 10\%$ for all

^a Both the parenterally administered once-weekly formulation of exenatide and QD liraglutide are under regulatory review with pending new drug applications; exenatide was granted US Food and Drug Administration approval in 2005 and is currently available only as a BID formulation.^{13,17,19}

AS = aspartate; BID = twice daily; CV = cardiovascular; DPP-4 = dipeptidyl peptidase-4; DURATION-1 = Diabetes Therapy Utilization: Researching Changes in A1C, Weight and Other Factors Through Intervention with Exenatide Once Weekly-1; E = exenatide; FBG = fasting blood glucose; FPG = fasting plasma glucose; FSG = fasting serum glucose; G = glimepiride; GL = glargine; GLP-1 = glucagon-like peptide-1; HbA1c = glycosylated hemoglobin; IN = insulin; L = liraglutide; LEAD = Liraglutide Effects and Actions in Diabetes; MET = metformin; PL = placebo; PO = by mouth; QD = once daily; QW = once weekly; R = rosiglitazone; ST = sitagliptin; SC = subcutaneous; SU = sulfonylurea; T2DM = type 2 diabetes mellitus; TZD = thiazolidinedione; Δ BL = change from baseline.

refer to means, and individual patients may have greater or lesser responses. Also, baseline HbA1c is a significant determinant of the potential HbA1c reduction. Higher baseline values drop more significantly than do baseline values that are closer to normal.

Weight reduction with GLP-1 receptor agonists. In addition to effective glucose lowering, the GLP-1 receptor agonists, particularly exendin-4 agonists, produced beneficial effects on weight (Table 1). Exenatide BID elicited mean weight reductions up to -3.6 kg at 30 weeks^{21,31,32} and -5.3 kg at 3.5 years.³⁷ Exenatide once weekly resulted in mean weight reductions of up to -3.8 kg at 15 weeks²² and -3.7 kg at 30 weeks.²¹ Effects on weight with liraglutide varied from a mean

reduction of up to -2.99 kg to a slight gain of up to $+0.13$ kg at 14 weeks^{40,41} and with weight loss of up to -2.8 kg at 26 weeks^{23,26} and up to -2.5 kg at 52 weeks.²⁵ In this review, only exenatide has been assessed in insulin-comparator studies, where it was shown to reduce weight compared with the insulin analogues, which led to weight gain.^{34–36}

Hypoglycemia. Patients receiving exenatide experienced lower rates of hypoglycemia (up to 17%) than patients treated with either insulin glargine or insulin aspart ($\sim 25\%$).^{34,36} The rate of hypoglycemia with exenatide is comparable to that seen with metformin (up to 21%) in a systematic review of oral antidiabetes agents conducted by the Agency for Healthcare Research and

TABLE 2**Effects of DPP-4 inhibitors on HbA1c, weight, and hypoglycemia in patients with T2DM**

Study	Study population/ duration of therapy	Study agents	HbA1c (mean Δ BL)	Weight (mean Δ BL)	Hypoglycemia
SITAGLIPTIN^a					
Aschner 2006 ⁴²	Monotherapy N = 741/24 wk	ST: 100 or 200 mg QD PO PL	ST: -0.61% to -0.76% PL: +0.18% ($P \leq .001$ vs PL)	ST: -0.1 kg to -0.2 kg (neutral effect) PL: -1.1 kg ($P < .001$)	ST vs PL: 1% vs 1%
Raz 2006 ⁴⁴	Monotherapy N = 521/18 wk, with inadequate glycemic control on diet and exercise	ST: 100 or 200 mg QD PO PL	ST: -0.36% to -0.48% PL: +0.12%	ST: -0.2 kg to -0.6 kg PL: -0.7 kg	ST vs PL: 1% vs 0%
Scott 2007 ⁴⁵	Monotherapy N = 743/12 wk	ST: 5, 12.5, 25, or 50 mg BID PO GLP: 5 mg/d PO (electively titrated up to 20 mg/d) PL	ST: -0.15% to -0.54% GLP: -0.76% PL: +0.23%	ST: +0.1 kg to +0.4 kg (relative to PL) GLP: +1.3 kg (relative to PL)	ST vs GLP vs PL: 2% vs 17% vs 2%
Nonaka 2008 ⁴³	Monotherapy, in Japanese patients N = 151/12 wk	ST: 100 mg QD PO PL	ST: -0.65% PL: +0.41% ($P < .001$)	ST: -0.1 kg PL: -0.7 kg	No hypoglycemic episodes with ST or PL
DeFronzo 2008 ³⁹	First clinical head-to-head study between a DPP-4 inhibitor and a GLP-1 receptor agonist, in MET-treated patients N = 61/crossover study with two treatment periods of 2 wk preceded by 1-wk PL lead-in and no interval washout	ST: 100 mg QD PO for 2 wk E: 5 μ g BID SC for 1 wk, then 10 μ g BID SC for 1 wk	ST: -19 mg/dL (FPG) E: -15 mg/dL (FPG) ($P = .3234$)	ST: -0.3 kg E: -0.8 kg ($P = .0056$)	No major hypoglycemic events with ST or E
Charbonnel 2006 ⁴⁶	N = 701/24 wk, added to ongoing MET therapy	ST: 100 mg QD PO PL	ST: -0.67% PL: -0.02% ($P < .001$)	ST: -0.6 kg to -0.7 kg PL: -0.6 kg to -0.7 kg (both $P < .05$ vs BL, but $P = .835$ between groups)	ST vs PL: 1% vs 2%
Rosenstock 2006 ⁵⁰	N = 353/24 wk; added to ongoing TZD (pioglitazone) therapy	ST: 100 mg QD PO PL	ST: -0.85% PL: -0.15%	ST: +1.8 kg PL: +1.5 kg ($P = \text{NS}$)	ST vs PL: 1% vs 0%
Hermansen 2007 ⁴⁷	In patients inadequately controlled with G or G + MET N = 441/24 wk	ST: 100 mg QD PO PL	ST: -0.45% PL: +0.28% ($P < .001$)	ST: +0.8 kg PL: -0.4 kg ($P < .001$)	ST vs PL: 12% vs 2%
Nauck 2007 ⁴⁸	In patients inadequately controlled with MET N = 1,172/52 wk	ST: 100 mg QD PO + MET $\geq 1,500$ mg/d GLP: 5 mg/d (titrated to 20 mg/d) + MET $\geq 1,500$ mg/d	ST: -0.67% GLP: -0.67%	ST: -1.5 kg GLP: +1.1 kg	ST vs GLP: 5% vs 32%
Raz 2008 ⁴⁹	Added to ongoing MET N = 190/30 wk	ST: 100 mg QD PO + MET $\geq 1,500$ mg/d PL + MET $\geq 1,500$ mg/d	ST: -1.0% PL: 0.0%	ST: -0.5 kg PL: -0.5 kg	ST vs PL: 1% vs 0%
SAXAGLIPTIN^a					
Chacra ⁵¹	Patients inadequately controlled with sulfonylurea N = 768/24 wk	SX: 2.5 or 5 mg/d + GLY 7.5 mg/d PL + GLY: 10 mg/d	SX: -0.54% to -0.64% GLY: +0.08% ($P = .0001$)	SX: +0.7 kg to +0.8 kg GLY: +0.3 kg	SX: 13.3% to 14.6% GLY: 10.1%
DeFronzo ⁵²	Patients inadequately controlled with MET N = 743/24 wk	SX: 2.5, 5, or 10 mg/d + MET PL + MET	SX: -0.59% to -0.69% MET: +0.13% ($P < .0001$)	SX: -0.53 kg to -1.43 kg MET: -0.92 kg	< 1% in all groups

Table continues on next page

TABLE 2 (continued)**Effects of DPP-4 inhibitors on HbA1c, weight, and hypoglycemia in patients with T2DM**

Study	Study population/ duration of therapy	Study agents	HbA1c (mean Δ BL)	Weight (mean Δ BL)	Hypoglycemia
Jadzinsky ⁵³	Treatment-naïve patients N = 1306/24 wk	SX: 5 or 10 mg/d + MET 500 mg/d SX: 10 mg + PL MET: 500 mg/d (MET titrated up to 2,000 mg/d)	SX + MET: -2.5% SX: -1.7% MET: -2.0% ($P < .0001$ vs monotherapy)	SX: -1.4 kg to -1.8 kg SX: -1.1 kg MET: -1.6 kg	$\leq 2\%$ in all groups
Rosenstock ⁵⁴	Treatment-naïve patients N = 401/24 wk	SX: 2.5, 5, or 10 mg/d PL	SX: -0.43% to -0.54% PL: +0.19% ($P < .0001$)	SX: -0.1 kg to -1.2 kg PL: -1.4 kg	None confirmed
Rosenstock ⁵⁵	Dose-ranging trial N = 338/12 wk (low-dose) N = 85/6 wk (high-dose)	Low dose: SX: 2.5, 5, 10, 20, 40 mg/d or PL High dose: SX: 100 mg/d or PL	Adjusted mean Δ Low dose: SX: -0.45% to -0.63% ($P = .9888$) PL: -0.27% High dose: SX: -1.09% PL: -0.36%	Not significant	Two mild cases in high-dose cohort
VILDAGLIPTIN^a					
Dejager 2007 ⁵⁶	Drug-naïve patients N = 632/24 wk	V: 50 mg QD PO V: 50 mg BID PO V: 100 mg QD PO PL	V: -0.8% to -0.9% PL: -0.3% ($P < .01$)	V: -0.3 kg to -1.8 kg PL: -1.4 kg	No hypoglycemic events with V 50 mg BID or PL; one hypoglycemic event for two patients on V 50 mg QD and one patient on V 100 mg QD
Pan 2008 ⁵⁹	Drug-naïve patients N = 661/24 wk	V: 100 mg/d, given as 50 mg BID PO A: Up to 300 mg/d, given TID PO	V: -1.4% A: -1.3%	V: -0.4 kg A: -1.7 kg ($P < .001$)	No hypoglycemic events with V or A
Pi-Sunyer 2007 ⁶⁰	Drug-naïve patients N = 354/24 wk	V: 50 mg QD PO V: 50 mg BID PO V: 100 mg QD PO PL	V: -0.5% to -0.8% PL: 0.0	V: 0.0 kg to -0.4 kg PL: -1.4 kg	No confirmed hypoglycemia reported
Schweizer 2007 ⁶¹	Drug-naïve patients with baseline HbA1c 7.5% to 11.0% N = 780/52 wk	V: 100 mg QD PO MET titrated to 2,000 mg QD PO	V: -1.0% MET: -1.4% ($P < .001$)	V: +0.3 kg MET: -1.9 kg ($P < .001$)	V vs MET: < 1% for each group
Garber 2007 ⁵⁷	Add-on to TZD (pioglitazone) therapy N = 463/24 wk	V: 50 mg QD PO V: 100 mg QD PO PL	V: -0.8% to -1.0% PL: -0.3%	V: +0.1 kg to +1.3 kg relative to PL PL: +1.4 kg	No severe hypoglycemic events reported with V or PL
Göke 2008 ⁵⁸	N = 463/52-wk extension of a previously published, multicenter, randomized, parallel-group study (Schweizer 2007 ⁶¹)	V: 100 mg QD PO MET: 2,000 mg QD PO	V: -1.0% MET: -1.5% ($P < .001$)	V: +0.5 kg MET: -2.5 kg	Only one confirmed hypoglycemic event reported with V

^a The orally administered sitagliptin was granted US Food and Drug Administration (FDA) approval in 2006; a single-tablet formulation of the combination of sitagliptin and metformin gained US FDA approval in 2007.^{17,19} Saxagliptin was approved by the FDA in 2009.²⁰ Although used in Latin America and the European Union, vildagliptin has yet to receive regulatory approval in the United States.¹⁸

A = acarbose; BID = twice daily; BL = baseline; DPP-4 = dipeptidyl peptidase-4; E = exenatide; FPG = fasting plasma glucose; G = glimepiride; GLP = glipizide; GLP-1 = glucagon-like peptide-1; GLY = glyburide; HbA1c = glycosylated hemoglobin; MET = metformin; PL = placebo; PO = by mouth; QD = once daily; SC = subcutaneous; ST = sitagliptin; SX = saxagliptin; TID = three times daily; T2DM = type 2 diabetes mellitus; TZD = thiazolidinedione; V = vildagliptin; Δ BL = change from baseline.

Quality.⁶² No major hypoglycemic events were reported in the liraglutide studies reviewed. The incidence of hypoglycemia reported with DPP-4 inhibitors (Table 2) is also low (2% or less in most studies). The glucose-dependent mechanisms of the incretin-based therapies minimizes the risk of hypoglycemia.

DPP-4 inhibitors and sustained HbA1c reduction. The effects of the DPP-4 inhibitors on HbA1c and weight, either as monotherapy or in combination with other agents, were evaluated in studies ranging in duration from 12 to 52 weeks (Table 2). No studies were identified that compared the glycemic control effects of DPP-4 inhibitors and insulin analogues. Sitagliptin led to a mean reduction in HbA1c from baseline of up to -0.65% at 12 weeks,^{43,45} up to -0.48% at 18 weeks,⁴⁴ up to -0.85% at 24 weeks,^{42,46,47,50} up to -1.0% at 30 weeks,⁴⁹ and up to -0.67% at 52 weeks.⁴⁸ Saxagliptin mean reductions in HbA1c ranged from -0.43% to -1.17% .^{51–54} Data from four 24-week T2DM studies^{56–60} showed vildagliptin reducing HbA1c up to -1.4% at 24 weeks, with the greatest reduction in a study that involved drug-naïve patients with a relatively short duration of disease (mean, 1.2 years).⁵⁹ Reductions in HbA1c of -1.0% were sustained in a 52-week study⁶¹ and its 52-week extension.⁵⁸

DPP-4 inhibitors: weight neutral. The DPP-4 inhibitors appear to have a weight-neutral effect (Table 2). The effects of sitagliptin on weight ranged from a loss of -1.5 kg⁴⁸ at 52 weeks to a gain of $+1.8$ kg at 24 weeks.⁵⁰ Weight changes with saxagliptin ranged from a mean reduction of -1.8 kg⁵³ to a gain of $+0.7$ kg.⁵¹ Two vildagliptin studies showed varying effects on weight ranging from a loss of up to -1.8 kg from baseline⁵⁶ to a gain of up to $+1.3$ kg⁵⁷ relative to placebo, both at 24 weeks.

Potential for CV risk reduction

Potentially beneficial effects on CV risk factors, including blood pressure (ie, reduction) and lipid concentrations (ie, differential effects on low-density lipoprotein and high-density lipoprotein cholesterol), were identified in seven GLP-1 receptor studies—three with exenatide (two with exenatide BID,^{37,38} and one with the investigational exenatide once weekly²¹) and four with liraglutide.^{23,25,26,41} For the DPP-4 inhibitors, three studies were identified—two with sitagliptin^{45,50} and one with vildagliptin⁶¹—in which potentially beneficial effects on CV risk factors were demonstrated. The data have been encouraging, although the clinical implications have yet to be fully understood.

Head-to-head comparison

A recent study compared the effects of the GLP-1 receptor agonist exenatide and the DPP-4 inhibitor sitagliptin on postprandial glucose (PPG) concentrations, insulin and glucagon secretion, gastric intake,

and caloric intake.³⁹ Although limited by a short treatment duration (2 weeks), the study showed that the GLP-1 receptor agonist had a greater effect than the DPP-4 inhibitor in reducing PPG concentrations, a more potent effect in increasing insulin secretion and decreasing postprandial glucagon secretion, and a relatively greater effect in reducing caloric intake; and that it decreased the rate of gastric emptying (sitagliptin had no effect). These differences suggest that exenatide may provide a greater degree of GLP-1 receptor activation than the more physiologic concentrations of GLP-1 reached with DPP-4 inhibition.³⁹ Results of a scintigraphic study showed that exenatide substantially slows the gastric emptying that is accelerated in patients with T2DM. This could be another beneficial mechanism in treating postprandial glycemia.⁶³

Adverse effects

Exenatide has shown effects on hepatic injury markers (ie, improvement in alanine and aspartate aminotransferases) for up to 3.5 years of treatment.³⁷ For the GLP-1 receptor agonist and DPP-4 inhibitor studies reviewed, the adverse events were generally mild and included nausea and vomiting, nasopharyngitis, and mild hypoglycemia.

Meta-analysis conclusions

The published clinical trial data presented in this review expand the body of evidence on the safety and efficacy of incretin-based therapy in patients with T2DM. These data include the results of a meta-analysis by Amori et al,¹⁷ which examined randomized controlled trials of 12 weeks' or longer duration that compared incretin-based therapy with placebo or other diabetes medications and reported HbA1c changes in adults with T2DM. The meta-analysis showed that incretin-based therapies reduced HbA1c more than placebo (weighted mean difference, -0.97% [95% confidence interval (CI), -1.13% to -0.81%] for GLP-1 receptor agonists and -0.74% [95% CI, -0.85% to -0.62%] for DPP-4 inhibitors) and were noninferior to other antidiabetes agents. Treatment with a GLP-1 receptor agonist (ie, exenatide) caused weight loss (-1.4 kg and -4.8 kg vs placebo and insulin, respectively) while DPP-4 inhibitors (ie, sitagliptin, vildagliptin) were weight neutral.¹⁷

Beta-cell function

Evidence regarding the effects of incretin-based therapies, particularly the exendin-4 GLP-1 receptor agonists, on beta-cell function in patients with T2DM continues to accumulate. When assessing long-term (1 year) exenatide treatment in patients with T2DM, a trial (n = 69) comparing exenatide with the basal insu-

lin analogue insulin glargine showed that exenatide and insulin glargine resulted in similar reductions in HbA1c (-0.8% vs -0.7% ; $P = .55$).⁶⁴ However, exenatide significantly reduced body weight while insulin glargine resulted in weight gain (-3.6 kg vs $+1.0$ kg; $P < .0001$). In terms of beta-cell function, arginine-stimulated C-peptide secretion during hyperglycemia increased 2.46-fold from baseline after 52 weeks of exenatide treatment compared with 1.31-fold with insulin glargine treatment ($P < .0001$).⁶⁴

With respect to the direct beta-cell effects of liraglutide, a preclinical study reported that liraglutide improved glucose homeostasis in marginal mass islet transplantation in diabetic mice.⁶⁵ In this study, liraglutide was shown, in a mouse model, to reduce the time to normoglycemia after islet cell transplantation (median time, 1 vs 72.5 days; $P < .0001$). The effects of liraglutide on beta-cell function also were assessed in 13 patients with T2DM. After 7 days of treatment, liraglutide improved beta-cell function, which was associated with improvement in glucose concentration.⁶⁶ Liraglutide improved potentiation of insulin secretion during the first meal, owing in part to restoration of the potentiation peak (which is markedly blunted in T2DM), in a phenomenon similar to that observed with exenatide.⁶⁷

Beneficial effects on beta-cell function have also been reported with DPP-4 inhibitors. In a model-based analysis of patients with T2DM, it was shown that sitagliptin improved basal, static, and dynamic responsiveness of pancreatic beta cells to glucose. The results were observed when sitagliptin was administered both as an add-on to metformin therapy and as monotherapy.⁶⁸ A 52-week, double-blind, randomized, parallel-group study compared vildagliptin 50 mg/day and placebo in 306 patients with T2DM and mild hyperglycemia (HbA1c, 6.2% to 7.5%). Vildagliptin was shown to significantly increase fasting insulin secretory tone, glucose sensitivity, and rate sensitivity, all of which are aspects of beta-cell function.⁶⁹

Summary

Based on the ability of incretin-based therapies to address various disease mechanisms, including beta-cell defects (ie, hyperglycemia), hormone-related abnormalities (ie, hyperglucagonemia, incretin deficiency/resistance), and accelerated gastric emptying (especially with GLP-1 receptor agonists); their favorable effects on weight (reduction with GLP-1 receptor agonists and neutral with DPP-4 inhibitors); their beneficial effects on CV risk factors; and their good safety profile (ie, hypoglycemia risk comparable with metformin), these agents could be considered therapeutic advances for the treatment of patients with T2DM.

INCRETIN-BASED THERAPIES IN GUIDELINES AND ALGORITHMS

The 2007 AACE medical guidelines for clinical practice for the management of diabetes recognized the place of the incretin-based therapies and included them among the pharmacologic options.⁵ Exenatide was specifically recommended for combination therapy with metformin, a sulfonylurea (secretagogue), a sulfonylurea plus metformin, or a TZD. Sitagliptin was recommended for use as monotherapy or in combination with metformin or a TZD.⁵

In 2009, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes convened a consensus panel to produce an algorithm for the initiation and adjustment of therapy for patients with T2DM. In this algorithm, GLP-1 receptor agonists were considered appropriate in certain clinical scenarios (eg, when hypoglycemia was an issue or weight loss was a major consideration during treatment). However, the groups also noted a need for more data on long-term safety and the cost of treatment with incretin-based therapies.⁷⁰

The AACE and the American College of Endocrinology recently developed “road maps” for managing patients with T2DM. In patients with T2DM who are naïve to therapy, DPP-4 inhibitors are among the recommended first options when the initial HbA1c is 6.0% to 7.0% and as a combination therapy component when HbA1c reaches 7.0% to 9.0%. In patients who have already received monotherapy for 2 to 3 months and whose HbA1c is 6.5% to 8.5%, treatment options include combination therapy with a DPP-4 inhibitor and metformin or a TZD. Another option includes the initiation of treatment with a GLP-1 receptor agonist in combination with a TZD, with metformin or a sulfonylurea, or with metformin and a sulfonylurea.⁷¹

The role of GLP-1 receptor agonist therapies and their incorporation into T2DM treatment algorithms was noted at the 2008 annual meeting of the ADA. In the Banting lecture, Ralph A. DeFronzo, MD, advocated the early use of triple-drug therapy with metformin, exenatide, and a TZD in the management of patients with T2DM.⁹

CONCLUSION

T2DM, which is linked to weight gain and obesity, is a complex disease that predisposes patients to and is associated with CVD. A better understanding and appreciation of the role of the incretin system in the pathogenesis of T2DM has led to the development of incretin-based therapies, such as the GLP-1 receptor agonists and DPP-4 inhibitors. As more experimental and clinical evidence becomes available, subtle nuances are emerging that distinguish the roles of these two therapeutic classes.

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Dr. Davidson reported that he wrote this article and received no assistance with content development from unnamed contributors. He reported that BlueSpark Healthcare Communications, a medical communications company, assisted with preliminary literature searches, reference verification, proofing for grammar and style, table and figure rendering based on author instructions, copyright permission requests, and identification of topical overlap with other manuscripts in this supplement.

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Redefining treatment success in type 2 diabetes mellitus: Comprehensive targeting of core defects

■ ABSTRACT

Despite advances in diagnosis and treatment, type 2 diabetes mellitus (T2DM), overweight/obesity, cardiovascular disease, and their sequelae are major public health burdens worldwide. The understanding of the pathophysiology of T2DM has traditionally emphasized decreased insulin secretion and increased insulin resistance, but evolving concepts now include the role of incretin hormones in disease progression. A comprehensive approach to managing patients with T2DM requires targeting both the fundamental defects of the disease and its comorbidities, including the sequelae of nonoptimal control of blood glucose, blood pressure, body weight, and lipids. Newer antidiabetes agents, such as the glucagon-like peptide-1 (GLP-1) receptor agonists and the dipeptidyl peptidase-4 (DPP-4) inhibitors, address fundamental defects related to glycemic control in T2DM and may have potential effects on other markers of cardiovascular risk. A redefinition of treatment success may be warranted as more data become available.

■ KEY POINTS

The NHANES 1999–2004 data showed that only 13.2% of patients with diagnosed diabetes achieved concurrent weight, blood pressure, and lipid level goals.

Among patients with T2DM, lifestyle intervention (control of weight, blood pressure, lipid levels) should be reinforced at every physician visit; glycosylated hemoglobin (HbA1c) should be monitored every 3 months until it is less than 7.0%, and then rechecked every 6 months.

The effects of GLP-1 agonists on HbA1c are comparable to insulin analogues, but GLP-1 agonists are associated with weight reduction, while insulin is associated with weight gain.

DPP-4 inhibitors have been associated with significant reductions in HbA1c when used alone or with metformin or pioglitazone.

According to the American Association of Clinical Endocrinologists (AACE) and the American Diabetes Association (ADA), glycosylated hemoglobin (HbA1c) in patients with diabetes should be maintained at 6.5% or less (AACE) or at less than 7.0% (ADA). Both organizations support an aggressive stepwise approach that includes medication and lifestyle modification, with strategies and clinical attention devoted to avoiding significant hypoglycemia.^{1,2} Yet, despite the introduction of new antidiabetes agents, most current management strategies are offset by limitations in achieving and maintaining glycemic targets needed to provide optimal care for patients with diabetes, more than 90% of whom have type 2 diabetes mellitus (T2DM).^{3,4}

Nationally, glycemic control among patients with T2DM has improved but is still far from optimal. According to data from the 1999–2000 National Health and Nutrition Examination Survey (NHANES), glycemic control (HbA1c < 7.0%) rates were 35.8% for patients with T2DM.⁵ In a more recent report (NHANES 1999–2004), fewer than half (48.4%) of adult patients with diagnosed diabetes achieved HbA1c levels below 7.0%.^{5,6} Factors contributing to these data include earlier onset and earlier detection of T2DM.⁷

■ CHANGING TREATMENT TRENDS

Available treatments for patients with T2DM include secretagogues, such as sulfonylureas and “glinides” (repaglinide and nateglinide), metformin, thiazolidinediones (TZDs), and dipeptidyl peptidase-4 (DPP-4) inhibitors among oral medications, and insulin and glucagon-like peptide-1 (GLP-1) receptor agonists among parenterally administered agents. According to the latest published data on prescribing patterns for patients with T2DM, analyses of the National Disease and Therapeutic Index (1994–2007) and the National Prescription Audit (2001–2007), sulfonylurea use decreased from 67% of treatment visits in 1994 to 34% of visits in 2007.⁸ By 2007, metformin, used in 54% of treatment visits, and TZDs, used in 28%, were the most frequently administered antidiabetes agents. Insulin use declined from 38% of visits during which a treatment was administered in

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1994 to 25% of visits in 2000, but had increased subsequently to 28% of visits in 2007.

SIGNIFICANCE OF CARDIOVASCULAR RISK

Clinical research has suggested that focusing solely on improving glycemic control may be insufficient to reduce overall morbidity and mortality associated with diabetes. Specifically, data from recent studies, including the Action to Control Cardiovascular Risk in Diabetes (ACCORD), the Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE), and the Veterans Affairs Diabetes Trial (VADT), emphasized that lowering HbA1c below 7% in a high-risk population of individuals with T2DM did not improve cardiovascular (CV) outcomes.^{9–11} The observations confirm that risk factors, including weight, blood pressure (BP), and lipid levels, are vitally important in reducing morbidity and mortality in this population. This perception is further underscored by the NHANES 1999–2004 data, which showed poor concurrent control of HbA1c, BP, and lipids; only 13.2% of patients with diagnosed diabetes achieved all three target goals simultaneously.⁶ Similarly, a nationwide survey in Norway showed that only 13% of patients with T2DM concurrently achieved goals for HbA1c, BP, and lipids.¹²

In the Danish Steno-2 Study, patients with T2DM and persistent microalbuminuria were treated with either intensive target-driven therapy using multiple drugs or conventional multifactorial treatment. Over a mean period of 13.3 years (7.8 years of treatment plus 5.5 years of follow-up), intensive multifactorial intervention to control multiple CV risk factors, including HbA1c, BP, and lipids, was associated with a lower risk of death from CV causes (hazard ratio [HR], 0.43; 95% confidence interval [CI], 0.19 to 0.94; $P = .04$) and a lower risk of CV events (HR, 0.41; 95% CI, 0.25 to 0.67; $P < .001$) than was conventional therapy.¹³

This article clarifies the redefinition of treatment success in patients with T2DM based on targeting the underlying physiologic defects of the disease.

T2DM, OVERWEIGHT/OBESITY, AND CV DISEASE: CLOSELY LINKED

The incidence and prevalence of T2DM, overweight/obesity, and CV disease (CVD) are increasing worldwide. It is estimated that the worldwide prevalence of diabetes will increase from 171 million in 2000 to 366 million by 2030¹⁴; T2DM increases the risk of morbidity and mortality from microvascular (eg, neuropathic, retinopathic, nephropathic) and macrovascular (eg, coronary, peripheral vascular disease) complications.¹⁵ According to a Michigan health maintenance organization study (N = 1,364), the median annual direct cost of medical care for Caucasian patients with T2DM who

were diet controlled, had a body mass index (BMI) of 30 kg/m² or higher, and had no vascular complications was estimated to be \$1,700 for men and \$2,100 for women.¹⁶ The actual cost of care for patients with T2DM may be much higher, since most patients present with multiple CV risk factors in addition to being overweight.

NHANES data show that approximately two-thirds of Americans are either overweight or obese¹⁷; overweight/obesity affects about 80% of adults diagnosed with T2DM.¹⁸ Overweight or obesity can increase the risk for developing T2DM by more than 90-fold and, in women, it can increase the risk for developing coronary heart disease (CHD) by sixfold.¹⁹ The close link between T2DM and CVD is underscored further with recent data from the Framingham Heart Study, which showed a high lifetime risk of CVD in patients with diabetes, heightened further by obesity. During the 30-year study period, the lifetime risk of CVD in normal-weight people with diabetes was 78.6% in men and 54.8% in women; the risk increased to 86.9% in obese men with diabetes and to 78.8% in obese women with diabetes.²⁰ The NHANES data also showed that the prevalence of T2DM increased in the past decade and that patients are being diagnosed at a younger age, from a mean age of 52 years in 1988–1994 to 46 years in 1999–2000.⁷

BRIDGING THE GAP FROM PATHOPHYSIOLOGY TO UNMET NEEDS

The paradigm behind the pathophysiology of T2DM has shifted from its perception as a simple “dual-defect” disease (ie, deficiency in insulin secretion and peripheral tissue insulin resistance) to a multidimensional disorder.^{1,21} This new model includes overweight/obesity, insulin resistance, qualitative and quantitative defects in insulin secretion, and dysregulation in the secretion of other hormones, including the beta-cell hormone amylin, the alpha-cell hormone glucagon, and the gastrointestinal incretin hormones GLP-1 and glucose-dependent insulinotropic polypeptide.^{21–23}

The major target of antidiabetes agents is glycemic control, assessed by a reduction in HbA1c, but their effects on other metabolic factors and their adverse effects differ with each agent (Table 1).³ Whereas metformin and alpha-glucosidase inhibitors may help normalize glycemia with weight-neutral effects, many other agents, including insulin and its analogues, the “glinides,” first- and second-generation sulfonylureas, and TZDs, are associated with weight gain.^{23,24} In addition, the propensity to induce hypoglycemia differs among agents and clearly reflects the mechanism of action of each drug. The observed limitations of older therapies treating a progressive disease that is associated with a number of comorbid conditions supports the need for continued development of new antidiabetes agents.

TABLE 1
Advantages and disadvantages of glucose-lowering interventions^a

Intervention	Advantages	Disadvantages
TIER 1: WELL-VALIDATED CORE³		
Step 1: Initial therapy		
Lifestyle to decrease weight and increase activity	Broad benefits	Insufficient for most within first year
Metformin	Weight neutral, minimal hypoglycemia	GI side effects, contraindicated with renal insufficiency
Step 2: Additional therapy		
Insulin	No dose limit, rapidly effective, improved lipid profile	One to four injections daily, monitoring, weight gain, hypoglycemia
Sulfonylurea	Rapidly effective	Weight gain, hypoglycemia (especially with glibenclamide or chlorpropamide)
TIER 2: LESS WELL-VALIDATED^{b,3}		
Thiazolidinedione	Improved lipid profile (pioglitazone)	Fluid retention, CHF, weight gain, bone fractures, potential increase in MI (rosiglitazone)
GLP-1 receptor agonist	Weight loss	Two injections daily, frequent GI side effects, long-term safety not established
Other therapy		
α-glucosidase inhibitor	Weight neutral	Frequent GI side effects, TID dosing
Glinide	Rapidly effective	Weight gain, TID dosing, hypoglycemia
Pramlintide	Weight loss	Three injections daily, frequent GI side effects, long-term safety not established
DPP-4 inhibitor	Weight neutral, minimal	Long-term safety not established hypoglycemia

^a "Well-validated core" and "less well-validated" are based on ADA/EASD consensus statement.³

^b In selected clinical settings, such as when hypoglycemia is particularly undesirable or where weight reduction is a major concern and glycosylated hemoglobin is close to normal, tier 2 (less well-validated) agents may be considered.

CHF = congestive heart failure; DPP-4 = dipeptidyl peptidase-4; GI = gastrointestinal; GLP-1 = glucagon-like peptide-1; MI = myocardial infarction; TID = three times daily

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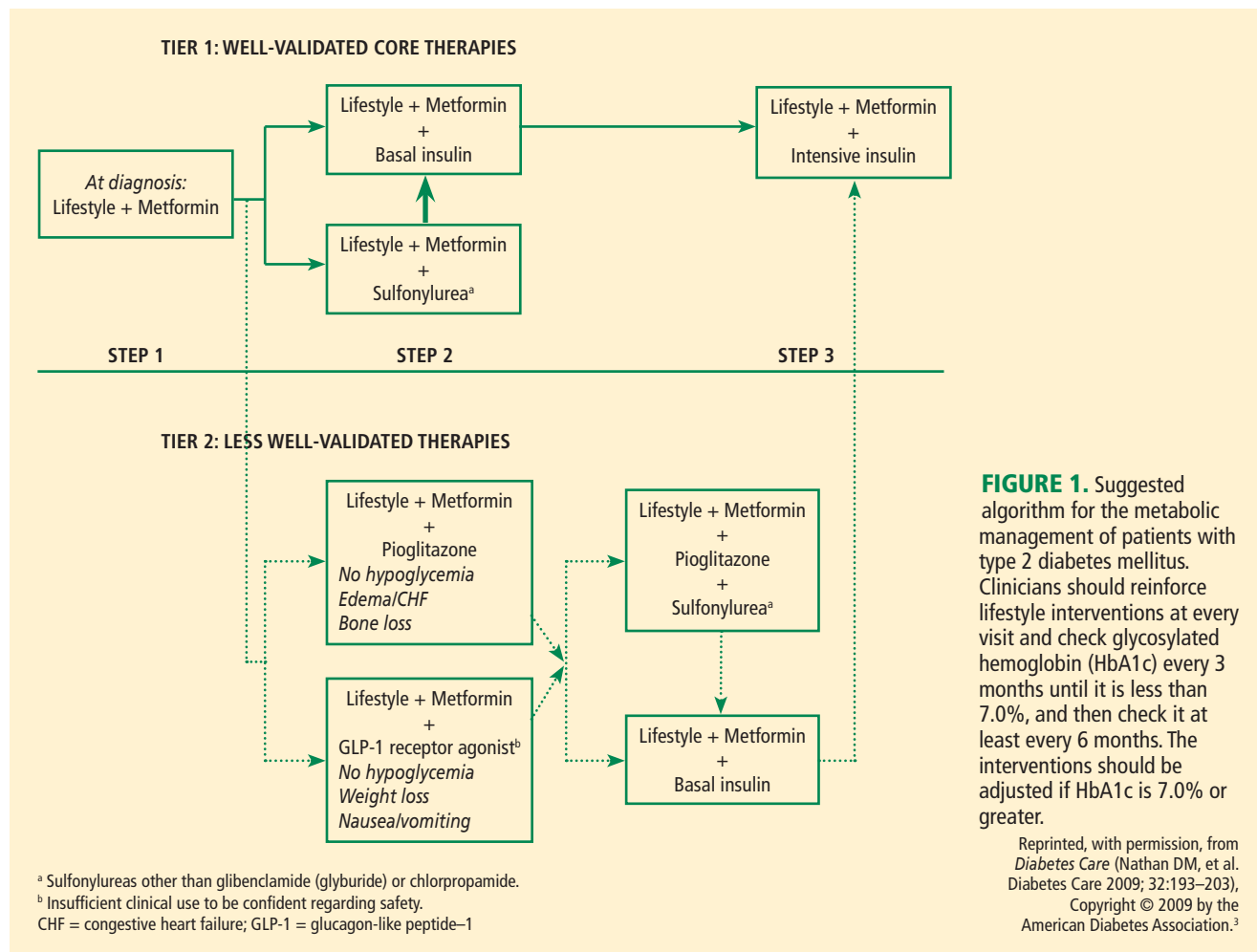
CLINICAL GUIDELINES AND CV RISK FACTOR MANAGEMENT

The best strategy for managing T2DM is a comprehensive approach that addresses the fundamental core defects plus associated factors that contribute to increased CV risk. Several specialty groups have suggested guidelines and algorithms for the management of T2DM and its comorbidities. These guidelines, including the ADA standards of medical care, the AACE standards in tandem with the American College of Endocrinology guidelines, and the recent joint statement from the ADA and the European Association for the Study of Diabetes (EASD), acknowledge that the core defects of T2DM and the associated CV risk factors (eg, weight gain, obesity, hypertension, dyslipidemia) are important in developing optimal treatment strategies.^{1–3} Medical nutrition guidelines advocate weight loss as a key initial step in managing T2DM and the comorbidities that lead to elevated CV risk.^{25,26} The National Institutes of Health and the US Department of Health and Human

Services/US Department of Agriculture advocate regular physical activity, dietary assessment, and periodic comorbidity and weight assessment for all people, not just those with T2DM or CVD.^{26,27}

Weight reduction

Evidence in support of effective lifestyle intervention was demonstrated in the Action for Health in Diabetes (Look AHEAD) study. After 1 year, patients with T2DM treated with intensive lifestyle intervention lost an average of 8.6% of their initial weight compared with 0.7% in patients treated only with diabetes support and education ($P < 0.001$). The intensive-intervention patients also had a significant drop in HbA1c (from 7.3% to 6.6%; $P < 0.001$) and were able to reduce their antidiabetes, antihypertensive, and lipid-lowering medications.²⁸ More recent data from the Look AHEAD study reported that overweight patients with T2DM enrolled in a weight management program experienced significant weight loss, improved physical



fitness, reduced physical symptoms, and overall improvement in health-related quality of life.²⁹ Thus, weight reduction appears to be a key component in reducing CV risk and improving quality of life in most patients with T2DM.^{28–30}

Hypertension

Hypertension is a major risk factor for microvascular complications and CVD, and may be associated with, or be the underlying result of, nephropathy.² BP control is clearly important in reducing the morbidity and mortality associated with T2DM. The recommended BP goal in patients with T2DM is less than 130/80 mm Hg.^{1,2}

Hyperlipidemia

According to the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III [ATP III]), diabetes is considered a CHD risk equivalent because it confers a high risk of new CHD developing

within 10 years.³¹ In addition to the NCEP–ATP III guidelines, the ADA and the AACE have set target levels for lipids in patients with diabetes, including T2DM.^{1,2,31} All three organizations have defined 100 mg/dL as the target level for low-density lipoprotein.

HbA1c and lifestyle intervention

The American Heart Association and the ADA initiated a call to action for global risk assessment for CVD and diabetes.³² According to their joint scientific statement, lifestyle intervention should be reinforced at every physician visit, and HbA1c should be monitored every 3 months until it is less than 7.0% and then rechecked every 6 months. Adjustments in intervention should be made if the HbA1c level is 7.0% or higher.³ A recent joint statement from the ADA and the EASD revised an earlier treatment algorithm for the initiation of therapy in patients with T2DM; the revision includes incretin therapies (ie, GLP-1 receptor agonists) as a tier 2 option, especially in patients in whom hypoglycemia and weight gain are concerns (Figure 1).³

EVOLUTION OF ANTIDIABETES THERAPIES

Traditional antidiabetes agents used in the treatment of patients with T2DM have focused mainly on insulin secretion and insulin resistance, with treatment success defined as achieving HbA1c goals with a reduced incidence of hypoglycemia.²³ Secretagogues, such as sulfonylureas and glinides, stimulate the pancreas to release insulin. Insulin sensitizers, such as TZDs and metformin, enhance the action of insulin in muscle and fat^{1,3,23} and lower hepatic glucose production. The alpha-glucosidase inhibitors alter carbohydrate absorption from the gastrointestinal tract.¹ The extent to which each agent achieves treatment success in terms of glucose lowering depends on several factors, including intrinsic attributes, duration of disease, and baseline glycemic control.³

Newer agents for the treatment of T2DM include the incretin-based therapies—GLP-1 receptor agonists and DPP-4 inhibitors—which influence mechanisms beyond increasing pancreatic insulin secretion and decreasing peripheral insulin resistance (Table 2).²² The GLP-1 signaling pathway has been leveraged by two distinct pharmacologic approaches. The first involves the use of synthetic peptides with glucoregulatory effects similar to those of endogenous GLP-1 (GLP-1 receptor agonists). The second involves the use of DPP-4 inhibitors, small molecules that inhibit the proteolytic activity of DPP-4, leading to enhanced endogenous GLP-1 concentrations.²²

GLP-1 receptor agonists

Exenatide effects. Although many agents are in development, to date exenatide is the only GLP-1 receptor agonist approved by the US Food and Drug Administration (FDA).^{8,33} Exenatide is an exendin-4 GLP-1 receptor agonist with multiple glucoregulatory effects, including enhanced glucose-dependent insulin secretion, reduced glucagon secretion and food intake, and slowed gastric emptying.^{22,34} Exenatide is detectable in the circulation for up to 10 hours following subcutaneous (SC) administration²² and has a greater potency in reducing plasma glucose than GLP-1 in preclinical studies.^{35,36}

By virtue of its beneficial effects on glycemic control, weight, BP, and lipids, exenatide addresses some of the components of the metabolic syndrome.^{37–41} In pivotal 30-week studies, exenatide was associated with HbA1c reductions that ranged from -0.40% to -0.86% from baseline and decreases in body weight of approximately -1 kg to -3 kg from baseline, without severe hypoglycemia.^{37–39} The percentage of patients who reached the ADA goal of HbA1c less than 7.0% at 30 weeks ranged from 24% to 34% . The addition of exenatide to TZD therapy in a 16-week study was associated with mean reductions in HbA1c of -0.98% , fasting plasma glucose (FPG) concentration of -1.69 mmol/L (-30.42 mg/dL), and body weight of -1.51 kg.⁴⁰

TABLE 2

Modes of action of incretin-based agents

Agent	Modes of action
GLP-1 receptor agonists	<p>Direct peptide binding to GLP-1 receptor</p> <ul style="list-style-type: none"> • Enhance meal-related insulin secretion in a glucose-dependent manner • Restore first-phase insulin secretory response to IV glucose • Suppress inappropriately elevated glucagon secretion • Regulate gastric emptying • Reduce food intake • Increase β-cell mass (animal models) and improve β-cell function (humans)
DPP-4 inhibitors	<p>Inhibit DPP-4 activity, thereby slowing the rate of endogenous incretin hormone degradation and facilitating their glucoregulatory effects</p> <ul style="list-style-type: none"> • Improve meal-related insulin secretion in a glucose-dependent manner • Suppress inappropriately elevated glucagon secretion • Increase β-cell mass (animal models) and improve β-cell function (humans)

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; IV = intravenous

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A posthoc analysis of an open-label extension study involving patients who completed the original 30-week placebo-controlled studies showed that 46% of patients who remained on exenatide achieved the ADA goal of HbA1c less than 7.0% at 3 years.⁴¹ Exenatide administered for up to 3.5 years was associated with sustained reductions in HbA1c of -1.0% ($P < .0001$) and body weight of -5.3 kg ($P < .001$). Pancreatic beta-cell function, assessed by homeostasis model assessment, improved, as did BP, triglyceride, high-density lipoprotein, low-density lipoprotein, and aspartate aminotransferase levels.⁴¹

Comparison with insulin analogues. Comparative studies have highlighted the contrasting effects of exenatide and insulin analogues (eg, insulin glargine and fixed-ratio insulin).^{42–45} In a 26-week trial comparing exenatide with insulin glargine in subjects with T2DM, both agents resulted in similar decreases in HbA1c. Exenatide was also associated with a -2.3 -kg weight reduction, whereas insulin glargine was associated with a $+1.8$ -kg weight gain.⁴² Although rates of symptom-

atic hypoglycemia were similar, there were fewer cases of nocturnal hypoglycemia with exenatide (0.9 event/patient-year vs 2.4 events/patient-year with insulin).

In a 32-week study comparing exenatide BID with titrated insulin glargine QD, the HbA1c reductions for exenatide and insulin glargine were comparable. However, body weight decreased -4.2 kg over two 16-week treatment periods with exenatide, but increased $+3.3$ kg over the same periods with the basal insulin analogue.⁴³ The incidence of hypoglycemia was lower with exenatide than with insulin glargine (14.7% vs 25.2%), although the difference was not statistically significant.

In another study that compared exenatide with biphasic insulin aspart, patients who were treated with exenatide also lost weight while those who received the fast-acting insulin analogue gained weight (between-group difference, -5.4 kg). Patients treated with exenatide also demonstrated greater reductions in postprandial plasma glucose (PPG) excursions following their morning ($P < .001$), midday ($P = .002$), and evening meals ($P < .001$).⁴⁴ Overall, hypoglycemia rates were similar at study end between exenatide and insulin aspart (4.7 events/patient-year vs 5.6 events/patient-year). In all of these studies, significant gastrointestinal adverse events (nausea and vomiting) occurred more frequently with exenatide, and more patients withdrew from exenatide than from insulin.

Formulations in development. Other advances in GLP-1 receptor agonist therapy include novel formulations under clinical development, such as exenatide once weekly^{36,46} and liraglutide, a human analogue GLP-1 receptor agonist formulated for once-daily administration.^{47,48} In a 52-week study in patients with T2DM, liraglutide significantly reduced HbA1c; the 1.2-mg SC QD dosage reduced HbA1c by -0.84% ($P = .0014$) and the 1.8-mg SC QD dosage by -1.14% ($P < .0001$). In comparison, glimepiride 8 mg orally QD achieved a -0.51% reduction. Liraglutide was also associated with greater reductions in weight, hypoglycemia, and systolic BP than glimepiride.⁴⁷

A 26-week study compared liraglutide (0.6, 1.2, and 1.8 mg SC QD), placebo, and glimepiride 4 mg QD in combination with metformin 1 g BID. HbA1c was reduced significantly in all liraglutide groups compared with placebo ($P < .0001$). Mean HbA1c decreased -1.0% with liraglutide 1.2 mg and 1.8 mg and with glimepiride; it decreased -0.7% with liraglutide 0.6 mg; and it increased $+0.1\%$ with placebo. Body weight decreased -1.8 kg to -2.8 kg in all liraglutide groups but increased $+1.0$ kg in the glimepiride group ($P < .0001$). The incidence of minor hypoglycemia with liraglutide ($\sim 3\%$) was comparable to that observed with placebo but less than that with glimepiride (17%; $P < .001$).⁴⁸

A once-weekly long-acting release (LAR) formulation of exenatide submitted to the FDA for approval

may provide enhanced glycemic and weight control, potentially improving patient acceptance and adherence.^{36,46} In a 15-week study, exenatide once weekly produced significant reductions in HbA1c, FPG, PPG, and body weight. There were no withdrawals due to adverse events, and the formation of anti-exenatide antibodies was not predictive of therapeutic end point response or adverse safety outcome. Instances of hypoglycemia were mild and not dose related.³⁶ In a 30-week study comparing exenatide LAR once weekly with exenatide BID, patients given exenatide LAR once weekly had significantly greater HbA1c reductions than did patients given exenatide BID (-1.9% vs -1.5% ; $P = .0023$). Treatment adherence was 98% with both exenatide regimens, and no episodes of major hypoglycemia occurred with either formulation regardless of background sulfonylurea use. Favorable effects on BP and lipid profile were observed with both exenatide regimens.⁴⁶

DPP-4 inhibitors

The DPP-4 inhibitors (commonly called gliptins) inhibit the proteolytic cleavage of circulating GLP-1 by binding to the DPP-4 enzyme, increasing the concentration of endogenous GLP-1 approximately two- to threefold.^{49–51} These concentrations result in more prompt and appropriate secretion of insulin and suppression of glucagon in response to a carbohydrate-containing snack or meal, with the change in glucagon correlating linearly with improved glucose tolerance.⁵¹

DPP-4 inhibitors, which are given orally, include sitagliptin and saxagliptin (approved in the United States) and vildagliptin (not approved in the United States but used in the European Union and Latin America).^{8,22,33,52} Sitagliptin can be used either as monotherapy or in combination with metformin or a TZD.^{8,49–55} Recently, a single-tablet formulation of sitagliptin plus metformin was granted regulatory approval.⁸

When used alone or in combination with metformin or pioglitazone, sitagliptin has been associated with significant reductions in HbA1c (of $\sim 0.5\%$ to 0.6% when used alone, $\sim 0.7\%$ with metformin, and $\sim 0.9\%$ with pioglitazone [$P < .001$ vs placebo]), with hypoglycemia occurring in 1.3% or less of the population.⁵⁴ In an 18-week study in which patients with T2DM who were inadequately controlled with metformin monotherapy were randomized to receive add-on sitagliptin (100 mg QD), rosiglitazone (8 mg QD), or placebo, sitagliptin reduced HbA1c -0.73% ($P < .001$ vs placebo) and reduced body weight -0.4 kg, while rosiglitazone reduced HbA1c -0.79% and increased body weight $+1.5$ kg.⁵⁵

To evaluate the effectiveness of sitagliptin and metformin as initial therapy, a 54-week study was completed in 885 patients with T2DM and inadequate glycemic control (HbA1c 7.5–11%) on diet and exercise.⁵⁶

Patients were evaluated on monotherapy with either sitagliptin (100 mg QD) or metformin (1 g or 2 g QD), or on initial therapy with the two in combination (sitagliptin 100 mg + metformin 1 mg or 2 mg QD). At week 54, in the all-patients-treated analysis, mean changes in HbA1c from baseline were -1.8% with sitagliptin plus metformin 2 g QD, -1.4% with sitagliptin plus metformin 1 g QD, -1.3% with metformin 2 g QD monotherapy, -1.0% with metformin 1 g QD monotherapy, and -0.8% with sitagliptin 100 mg QD monotherapy.

All treatments improved measures of beta-cell function (eg, homeostasis model assessment [HOMA]-beta, proinsulin/insulin ratio). Mean body weight decreased from baseline in the combination and metformin monotherapy groups and was unchanged from baseline in the sitagliptin monotherapy group. The incidence of hypoglycemia was low (1% – 3%) across treatment groups. The incidence of gastrointestinal adverse experiences was evaluated with the coadministration of sitagliptin and metformin and appeared similar to that observed with use of metformin as monotherapy.⁵⁶ Thus, this study suggested that an initial combination of a DPP-IV inhibitor with metformin can improve glycemic control and markers of beta-cell function in patients with T2DM.

Incretin-based therapies compared

Studies in both healthy individuals and in patients with T2DM have shown that oral DPP-4 inhibitors such as sitagliptin increase endogenous GLP-1 concentrations by about twofold compared with placebo.^{22,50} The pharmacologic concentration of subcutaneously administered exenatide available for activating the GLP-1 receptor is significantly greater than the increased endogenous GLP-1 concentrations achieved with sitagliptin. In a recent clinical study comparing exenatide and sitagliptin in patients with T2DM, the mean 2-hour plasma concentration for exenatide was 64 pM compared with the mean 2-hour postprandial GLP-1 concentration of 15 pM for sitagliptin (baseline GLP-1 concentration was 7.2 pM).⁵⁷ While both agents were shown to be effective, exenatide appeared to have had a greater effect than sitagliptin in increasing insulin secretion and reducing postprandial glucagon secretion, leading to significantly ($P < 0.0001$) greater reductions in PPG.⁵⁷

Sitagliptin has been minimally associated with nausea, whereas patients who take exenatide need to be informed of the risk of usually mild to moderate, but sometimes severe, nausea and vomiting that tends to decrease over time.

For a detailed comparison of the effects of GLP-1 receptor agonists and DPP-4 inhibitors on HbA1c, weight, and hypoglycemia, see “Advances in therapy for type 2 diabetes: GLP-1 receptor agonists and DPP-4 inhibitors,” page S28.

CONCLUSION

Despite advances in diagnosis and treatment, T2DM, overweight/obesity, CVD, and their complications remain major public health burdens worldwide. The concepts that explain the pathophysiology of T2DM include the contribution of various factors beyond insulin secretion and insulin resistance, such as the role of incretin hormones in disease progression. A comprehensive approach to managing patients with T2DM requires targeting the fundamental defects of the disease and its comorbidities. Newer agents, including incretin-based therapies such as GLP-1 receptor agonists and DPP-4 inhibitors, address the fundamental defects of T2DM. The definition of treatment success in the management of T2DM will be redefined as more data become available on agents that exert beneficial effects not only on glycemia but on parameters that may influence overall CV health, such as weight, BP, and lipid profiles.

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