Approximately two thirds of patients with type 2 diabetes mellitus (T2DM) are unable to reach the hemoglobin A\textsubscript{1c} target set by the American Diabetes Association (HbA\textsubscript{1c}<7.0%). Therefore, T2DM continues to be a major public health concern. Incretin mimetics and dipeptidyl peptidase IV inhibitors are medications that have the potential to improve patients’ glycemic control, as well as to result in beneficial socioeconomic effects. Research suggests that significant benefits are to be gained from incretin mimetics and dipeptidyl peptidase IV inhibitors, either one used as monotherapy or used together as combination therapy. However, the benefits and risks of these agents need to be evaluated more thoroughly, with emphasis on such adverse effects as edema, hypoglycemia, and weight gain.

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**Application of Incretin Mimetics and Dipeptidyl Peptidase IV Inhibitors in Managing Type 2 Diabetes Mellitus**

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The effective management of type 2 diabetes mellitus (T2DM) continues to pose a challenge to physicians. Despite the development and use of several medications to control patients’ blood glucose levels, two thirds of patients with T2DM remain unable to reach the hemoglobin A\textsubscript{1c} (HbA\textsubscript{1c}) target of less than 7.0% set by the American Diabetes Association.\textsuperscript{1,2} Thus, T2DM continues to be a major public health concern. Newer treatment agents, such as incretin mimetics and dipeptidyl peptidase IV (DPP-IV) inhibitors, have the potential to improve patients’ glycemic control, as well as to result in beneficial socioeconomic effects.\textsuperscript{3,7}

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**Targets for Management of Type 2 Diabetes Mellitus**

Although the American Diabetes Association recommends a target HbA\textsubscript{1c} level of less than 7%, it notes that a level of 6% would be preferable if safely achievable.\textsuperscript{8} In order to achieve such HbA\textsubscript{1c} targets, patients must also reach desirable fasting glucose levels (90 mg/dL-130 mg/dL) and postprandial glucose levels (<180 mg/dL).\textsuperscript{8} A primary clinical target is to control the fasting glucose concentration.

The National Health and Nutrition Examination Survey (NHANES) analyzed T2DM targets in two patient populations—one with 1215 patients studied from 1988 to 1994 and another with 372 patients studied from 1999 to 2000.\textsuperscript{1,2} After treatment with insulin, oral antidiabetic drugs, or diet, less than 45% of the combined patient population achieved the HbA\textsubscript{1c} target of less than 7%. The low-density cholesterol (LDL-C) targets of less than 100 mg/dL in both and women were achieved by about 36% of the patients, while the high-density lipoprotein (HDL-C) targets of 40 mg/dL in men and 55 mg/dL in women were reached by 30% of the patients. Triglyceride concentrations reaching the target of less than 150 mg/dL were achieved by about 65% of the patients. The blood pressure target of 130/80 mm Hg was achieved in about 40% of the population treated with blood pressure–lowering agents.\textsuperscript{2} Therefore, the NHANES study showed that many patients with T2DM have trouble achieving healthcare targets beyond just those associated with glycemic control.

**Pharmacologic Interventions**

The availability of new drugs for hypertension steadily increased between the 1950s and the year 2000. The advent of vasodilator compounds was followed by adrenergic neuronal blocking agents and diuretics. Centrally acting \(\alpha\)-agonists, such as clonidine, became available before \(\beta\)-blockers and \(\alpha\)-agonists and \(\alpha\)-antagonists in the 1970s. Calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin-receptor blockers began to appear in the 1980s and 1990s, later followed by the renin inhibitors.

For T2DM, the development of new drugs remained relatively flat from the 1960s to the 1980s, with sulfonylureas...
Healthy blood glucose levels are dependent on the dynamic processes of hepatic production of glucose and skeletal muscle use of glucose. These dynamic processes include the suppression by insulin of glucose production in the liver, and the secretion of glucagon by the α cells of the pancreas. Thus, there are three potential targets in the management of hyperglycemia in patients: excessive hepatic production of glucose, insufficient skeletal muscle disposal of glucose, and excessive pancreatic production of glucagon. Treatment strategies designed to improve these processes will result in improvements in a patient’s glycemic status.

Managing Glucose Production and Use
Data from the Diabetes Prevention Program were used by the US Department of Health and Human Services to recommend that adults exercise for a minimum of 30 minutes per day. Such an exercise program will improve skeletal muscle mass, the capacity for clearing glucose, and, ultimately, insulin sensitivity. Unlike natural incretins, however, exenatide is resistant to degradation by DPP-IV. Thus, it shows much promise for treating patients with T2DM.
Figure 1 displays results of three 30-week clinical trials that examined the effects of exenatide in patients with T2DM who were also using metformin (N = 336), sulfonylurea (N = 377), or metformin plus sulfonylurea (N = 733). Exenatide was given to patients 15 to 60 minutes before two large meals. Patients using metformin who were also treated with 10 g of exenatide twice a day had a further reduction of HbA1c of approximately 0.8%, compared with patients using metformin and placebo (P < .001). The sulfonylurea-exenatide group and the metformin-sulfonylurea-exenatide group also had further reductions in their HbA1c levels of about 0.8% compared with their corresponding placebo groups (P < .001). The percentages of patients who completed the study using 10 g of exenatide and who reached the target HbA1c level of less than 7.0% were the following: approximately 46% in the metformin-exenatide group, 41% in the sulfonylurea-exenatide group, and 34% in the metformin-sulfonylurea-exenatide group (Figure 2). The lesser reduction in the latter, combined group might be explained by the fact that T2DM was longer standing in those patients, thereby resulting in greater loss of endogenous insulin secretion.

Blonde et al studied 314 overweight patients with T2DM who used exenatide for 82 weeks. The first 30 weeks of the study were placebo-controlled. Fifty-two additional weeks were an open-label uncontrolled extension. At week 30, patients using 10 g of exenatide twice a day had an average reduction in body weight of 2 kg from baseline, in conjunction with an improvement in HbA1c levels of about 0.8%. Approximately 50% of the patients using exenatide had a neutral response. Therefore, this study suggests that about half of the patients using exenatide can expect to achieve a significant weight loss with the drug.

Blonde et al also demonstrated that the body mass index (BMI) of patients with T2DM predicts their degree of weight loss when using exenatide. Patients with the greatest BMI (>40) also had the greatest weight loss during the 82-week course of the study—approximately 8 kg.

Heine et al conducted a 26-week randomized controlled trial to compare glargine insulin (one daily dose to maintain fasting glucose levels) with exenatide (10 g twice a day). Patients with suboptimally controlled T2DM and a mean baseline HbA1c level of 8.2% were randomly assigned to receive either glargine insulin (n = 260) or exenatide (n = 275). At week 26, the average dose of glargine insulin was 25 units per day, a relatively small dose of insulin for most patients with T2DM.

Heine et al found that the patients’ average HbA1c levels fell to just above 7% in both groups (1.1% drop from the baseline). The body weight of patients using glargine insulin increased an average of 1.8 kg during the study, while that of patients using exenatide decreased an average of 2.3 kg. Thus, the study suggested that glargine insulin and exenatide produce similar benefits in HbA1c levels, but exenatide has the added benefit of weight loss. In addition, measurements of preprandial glycemic and postprandial glycemic excursions indicated a tendency for patients using exenatide to have reduced postprandial glycemic excursions.

The differences in adverse effects between glargine insulin and exenatide are striking. Heine et al found that nausea occurred in about 9% of patients using glargine insulin, while it occurred in 57% of patients using exenatide. Vomiting occurred in about 4% of patients using glargine insulin and 17% of patients using exenatide (P < .001). The hypoglycemia rate in both groups was comparable, with 6.3 events per patient-year in the glargine group and 7.3 events per patient-year in the exenatide group.
Incretin Mimetics: Liraglutide

Liraglutide is a long-lasting incretin mimetic that is currently under investigation.17,18 It is a receptor agonist like exenatide; it is an analog of GLP-1 that is DPP-IV resistant. In a 12-week controlled trial by Madsbad et al,17 193 patients with T2DM resistant to exenatide; it is an analog of GLP-1 that is DPP-IV resistant. In a 12-week controlled trial by Raz et al 24 in which 521 patients with T2DM were evenly randomly assigned to receive one of five dosages of liraglutide (0.045 mg once a day to 0.75 mg once a day), the sulfonylurea glimepiride, or placebo. Both liraglutide and glimepiride produced comparable reductions in HbA1c, and fasting glucose levels. However, glimepiride use led to increases in body weight, while liraglutide led to decreases in weight. The reduction in HbA1c level by liraglutide was dose-dependent, with the lowest dosage failing to lead to a decrease in HbA1c level.

Dipeptidyl Peptidase IV Inhibitors

Glucagon-like peptide 1 is synthesized in the villi of the epithelium of the small intestine. Immediately after synthesis, GLP-1 can be acted on by DPP-IV. The DPP-IV inactivation process causes greater than 50% inactivation of GLP-1 within 1 to 2 minutes—before the GLP-1 reaches general circulation.19-23 Dipeptidyl peptidase IV inhibitors are drugs that block the action of this degradation pathway. By blocking this action, DPP-IV inhibitors can lead to an increase in endogenous GLP-1 concentration, benefiting patients with T2DM. Several DPP-IV inhibitors are under development.24-31

Table 1 presents the results of an 18-week trial by Raz et al24 in which 521 patients with T2DM were randomly assigned to receive monotherapy with one of two different dosages of the DPP-IV inhibitor sitagliptin (100 mg once a day or 200 mg once a day) or placebo. At week 18, the placebo-subtracted HbA1c reductions in patients taking sitagliptin were 0.6% in the group assigned to 100 mg once a day and 0.48% in the group assigned to 200 mg once a day (P<.001). Approximately 33% of the patients with T2DM achieved the HbA1c target of less than 7%. Patients with higher baseline HbA1c levels had greater HbA1c reductions with sitagliptin. If the patients’ baseline HbA1c levels were less than 8%, the reductions of HbA1c were 0.44% in the group assigned to 100 mg once a day and 0.33% in the group assigned to 200 mg once a day. If the baseline HbA1c levels were greater than 9%, the reductions of HbA1c were 1.2% in the group assigned to 100 mg once a day and 1.04% in the group assigned to 200 mg once a day.

Postprandial glucose levels in patients with T2DM taking sitagliptin for 18 weeks were reduced approximately 40 mg/dL in the group using 100 mg once a day and 50 mg/dL in the group using 200 mg once a day.24 The 2-hour postprandial glucose reduction in patients taking sitagliptin reached statistical significance compared with placebo (P < .001). This result was most likely caused by a reduction in postprandial hyperglucagonemia.

Research into using sitagliptin is influenced by current concepts regarding β cells. The β cells of the pancreas are believed to have a lifespan of approximately 7 years. Precursors to β cells are stem cells. If these precursor cells fail to differentiate into new β cells, T2DM may develop in patients at an age of approximately 50 years.23 Table 1 shows a reduction in the proinsulin-insulin ratio—a marker of insulin secretion and β-cell function—in patients who received either dosage of sitagliptin for 18 weeks.24 In addition, the results of the homeostasis model assessment (HOMA) also indicated an increase in β-cell function with both dosages of sitagliptin (Table 1).

Therefore, the 18-week study by Raz et al24 demonstrated significant benefits of sitagliptin in improving β-cell function; HbA1c levels; postprandial glucose excursions; postprandial insulin levels; and the proinsulin-insulin ratio.

Charbonnel et al25 reported on 701 patients who were randomly assigned to receive either sitagliptin (100 mg once a day) or placebo in addition to their glucose-lowering medication. The placebosubtracted reductions in HbA1c with sitagliptin were 0.60% (95% CI: -0.82 to -0.39) in the group assigned to 100 mg once a day and 0.48% (95% CI: -0.70 to -0.26) in the group assigned to 200 mg once a day. In the two dosage groups, there were no differences in the occurrence of adverse events or withdrawals due to adverse events. Therefore, sitagliptin is well tolerated at both dosages.
ongoing regimen of metformin. This 24-week add-on study showed that patients taking sitagliptin had an additional HbA1c decline of 0.65%, an additional fasting plasma glucose decline of about 25 mg/dL, and an additional 2-hour postprandial glucose reduction of about 50 mg/dL, compared with placebo (P < .001) (Table 2). The patients using sitagliptin also had reductions in their proinsulin-insulin ratio; increases in their C-peptide, fasting insulin, and postprandial insulin; and increases in their (β)-cell function as indicated by the HOMA (Table 2).25

In a 24-week trial reported by Rosenstock at al26, 30 mg to 45 mg of sitagliptin added to a regimen of pioglitazone led to a reduction in HbA1c of <0.7% in patients with inadequately controlled T2DM, compared with placebo. Approximately 45% of the patients using sitagliptin sustained an HbA1c level of less than 7% through the duration of study.

A second DPP-IV inhibitor that has been investigated is vildagliptin. A 12-week monotherapy study by Pratley et al27 compared patients with T2DM receiving 25 mg of vildagliptin twice a day (n = 70) with those receiving placebo (n = 28). The group receiving vildagliptin had a reduction in HbA1c of approximately 0.6% compared with the group receiving placebo (P < .001). The fasting glucose levels of the group using vildagliptin were also improved over those in the group using placebo.

According to Schweizer et al,28 drug-naive patients with T2DM who received 1 year of treatment with 50 mg of vildagliptin twice a day (n = 526) and patients receiving metformin had a significant sustained decrease in HbA1c of about 1%, compared with patients receiving metformin (n = 254). The group using vildagliptin had a 1.0% reduction in HbA1c compared with baseline (P < .001), and the group receiving metformin had a 1.4% decrease from baseline (P < .001).28

Rosenstock et al29 compared dosages of 50 mg of vildagliptin twice a day (n = 459) with 8 mg of rosiglitazone once a day (n = 238) in a 24-week trial of patients with T2DM. Both vildagliptin and rosiglitazone resulted in comparable reductions in HbA1c of more than 1% from baseline. Patients using rosiglitazone, however, had an average increase in body weight of 1.5 kg at the end of the study, while patients using vildagliptin had an average decrease in weight of 0.3 kg. Rosenstock et al29 noted that the loss in body weight with vildagliptin was not statistically significant. According to them, the glitpins will most likely remain weight-neutral medications with glucose-lowering properties, providing a probable advantage over existing thiazolidinediones.

Treatment of patients with T2DM with a vildagliptin-metformin combination (50 mg of vildagliptin once daily, 1500 mg-3000 mg of metformin once daily) was compared with a placebo-metformin combination in a 12-week open-label feasibility study and 40-week extension by Ahren et al.30 During the first 12 weeks, the group treated with the vildagliptin-metformin combination (n = 56) showed a reduction in HbA1c levels. This reduction continued throughout the extension. By contrast, the group using the placebo-metformin combination (n = 51) showed a sustained increase in HbA1c levels after week 4.

### Table 2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo-Subtracted Change With Sitagliptin Plus Metformin</th>
<th>Other Effects of Sitagliptin Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c %</td>
<td>-0.65</td>
<td>Decreased proinsulin-insulin ratio</td>
</tr>
<tr>
<td>Fasting plasma glucose, mg/dL</td>
<td>-25.4</td>
<td>Increased fasting insulin, C-peptide, postmeal insulin</td>
</tr>
<tr>
<td>Two-hour postmeal plasma glucose, mg/dL</td>
<td>-50.6</td>
<td>Increased HOMA-β (measure of β-cell function)</td>
</tr>
</tbody>
</table>

Abbreviation: HOMA, homeostasis model assessment.

* Patients were randomly assigned (1:2) to receive addition of placebo or 100 mg of sitagliptin once a day to ongoing metformin therapy for 24 weeks.
This study provided an opportunity to assess and compare the durability of vildagliptin and metformin in patients. At the end of 1 year of treatment, the patients using vildagliptin with metformin had a decline of approximately 1.1% in their HbA\textsubscript{c} levels compared with the patients using placebo with metformin ($P < .001$). The reduction in HbA\textsubscript{c} compared with baseline was 0.6% in the group treated with the vildagliptin-metformin combination.

Fonseca et al\textsuperscript{13} studied 125 patients with T2DM who were given 50 mg of vildagliptin twice a day in addition to insulin for a 24-week core study, which was followed by a 28-week extension. This group was compared with 131 patients with T2DM receiving placebo and insulin. The group receiving vildagliptin had a reduction in HbA\textsubscript{c} levels from approximately 8.5% at baseline to 7.9% at week 52. Furthermore, adding 50 mg of vildagliptin once a day to the placebo arm during the extension period also produced a reduction in HbA\textsubscript{c} levels. The study indicated that using vildagliptin once a day may be more efficacious in reducing HbA\textsubscript{c} levels than using it twice a day, though the difference in results between the two dosages was not statistically significant.

### Incretin Mimetics Compared With Dipeptidyl Peptidase IV Inhibitors

The administration routes and physiologic effects of incretin modulators (ie, incretin mimetics and DPP-IV inhibitors) are compared in Figure 3. The major difference between incretin mimetics and DPP-IV inhibitors is that incretin mimetics are administered by injection, whereas DPP-IV inhibitors are administered orally. After the injection of incretin mimetics, there is an increased and sustained level of GLP-1 in the patient’s circulation, but after the oral administration of DPP-IV inhibitors, the level of GLP-1 increases only at mealtime. Incretin mimetics produce weight loss in patients, whereas DPP-IV inhibitors are weight neutral. No nausea is associated with DPP-IV inhibitors, but research indicates that 13% to 19% of patients using incretin mimetics have nausea during 1 to 2 months after beginning treatment.

### References


(continued)


