Initiating a Glucagon-like Peptide-1 Receptor Agonist in the Management of Type 2 Diabetes Mellitus

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Control of blood glucose levels and restoration of pancreatic islet function are among the goals of physicians seeking to improve outcomes in patients with type 2 diabetes mellitus (T2DM). A growing body of evidence supports the use of incretins to achieve these goals, and current guidelines recommend earlier and more frequent use of these agents. However, in patients with T2DM, treatment paradigms should always be individualized. The author discusses issues for physicians to consider when adjusting T2DM therapy, including patient comorbidities, glucose control patterns, and potential adverse effects. The importance of patient education and practical points for initiating a glucagon-like peptide-1 receptor agonist are also reviewed.

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eral types of cells that produce metabolic hormones, including β cells that produce insulin and α cells that produce glucagon. Insulin and glucagon both play important roles in maintaining blood glucose levels, making the pancreatic islets important control centers for the regulation of glucose metabolism. A growing body of research has demonstrated that incretins improve islet function.5

Current guidelines and treatment algorithms include earlier and more frequent use of incretins than previously recommended.6-9 These guidelines are a helpful starting point for treatment and provide physicians with evidence-based treatment options. However, treatment should always be individualized for patients with T2DM. Incretin-based therapies are especially helpful in the treatment of patients who need body-weight management or who are at risk for treatment-related hypoglycemia.

Important Elements of Screening and Safety
As T2DM progresses in duration and severity, metformin, the most widely used oral antihyperglycemic monotherapy, gradually becomes less effective.10 This decline in efficacy is understandable, because metformin partially addresses insulin resistance but does not effectively address the problem of progressive decline in β-cell function. Nor does metformin generate clinically significant weight reduction in overweight or obese patients with T2DM when these patients need to take combinations of glucose-lowering agents to maintain glycemic control.11

Physicians should provide appropriate patient education about the pathophysiologic development and natural history of diabetes mellitus, as well as the mechanisms of action of medications used to control glucose levels. If patients understand early in the course of their disease that worsening glycemic control is most likely the result of decreased β-cell function, they will understand how changes in their treatment regimen are likely to improve glucose levels. This approach to education should focus on the current overall status of the patient’s disease, including the presence and severity of additional conditions and the most appropriate medications within that context. In this way, patients will become aware that improved glycemic control is possible with newer agents that do not carry the risk of worsening underlying conditions or adverse events.

When adjusting a patient’s treatment, it is necessary to consider many issues, including blood glucose measurements, comorbidities, and medication adverse effects. These assessments should begin with a comprehensive review of glucose patterns. The relative contributions of fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) levels to overall glycemia depend on the level of HbA1c. When the level of HbA1c is near normal, the contribution of PPG is proportionally greatest.12 The PPG contribution diminishes as the HbA1c level rises above 8.0%, when the contribution of FPG becomes more predominant.12

When metformin monotherapy fails to maintain glycemic control, the optimal second-line agent should be individually determined. As a practical matter, incretin-based agents should be considered in patients whose disease is of relatively short duration or when the likelihood of residual β-cell function is a factor. Incretin-based agents also stimulate insulin secretion and suppress glucagon secretion in a glucose-dependent manner,13 thereby reducing PPG elevations.14

If the patient is already taking several oral medications, it is important for the physician to consider what additional help an incretin-based agent might provide. For example, clinical trials have demonstrated the usefulness of GLP-1 receptor agonists in further reducing glucose levels in the presence of combination therapy with metformin and sulfonylureas.15,16 An important caveat in this situation is that the presence of a sulfonylurea may heighten the possibility of a hypoglycemic reaction when a GLP-1 receptor agonist is concomitantly administered, usually resulting in the need to lower the dose of the sulfonylurea.15,16 The algorithm developed by the American Association of Clinical Endocrinologists strongly encourages physicians to use combination agents that have complementary mechanisms of action—prudent advice for optimizing the benefit of additional medications.6

Renal Impairment
In addition to the current explosive epidemic of T2DM, it is equally clear that we are experiencing an epidemic of chronic kidney disease—among the most common comorbidities in patients with T2DM, especially those with concomitant hypertension.17 Assessment of kidney function is essential before initiation of GLP-1 receptor agonist therapy. Liraglutide, a long-acting GLP-1 receptor agonist given once daily, has no required dosage adjustment in the presence of chronic kidney disease.18 However, exenatide, the first available GLP-1 receptor agonist, has a shorter half-life, requiring twice-daily dosing and dose adjustment in patients with renal impairment.19

Exenatide should not be used in patients with severe renal impairment or end-stage renal disease, and it should be used with caution in patients who have undergone renal transplantation.3 Caution should be applied when initiating exenatide or when escalating the exenatide dose in patients with moderate renal failure.19 Renal insufficiency and acute renal failure have occurred with exenatide in patients who have preexisting kidney disease or who are taking other drugs with a potential for nephrotoxicity.19 To date, no such renal toxicity has been reported with liraglutide.4

It should be noted that in studies with laboratory rats, thyroid C-cell carcinomas developed with high doses of liraglutide (ie, 8 times the clinical dose).18 In human trials, thyroid C-cell hyperplasia has been observed with liraglutide use, but no human carcinomas have been reported to date.4 Nevertheless, the US Food and Drug Administration requires a black box warning about the risk of thyroid cancer in patients treated with liraglutide.4

Pancreatitis
Pancreatitis has been reported with exenatide and with liraglutide. Thus, it is important to screen patients carefully for a history of pancreatitis or for risk factors for pancreatitis.20 People with diabetes mellitus are more likely to have a number of risk factors for acute pancre-
atitis, including gallstones, hypertriglyceridemia, and heavy drinking—the most common causes of pancreatic inflammation.\textsuperscript{2,21} Even when these conditions were taken into account, diabetes mellitus itself was linked to an 89% increase in the risk of acute pancreatitis.\textsuperscript{21}

In patients with diabetes mellitus, these findings necessitate caution and close monitoring when any agents are used that might carry a higher risk of pancreatitis. When such drugs are used, patients should be made aware of the signs and symptoms of the onset of pancreatitis (eg, sudden, severe upper abdominal pain that becomes worse after eating or when lying flat; nausea; fever). Patients should also be given guidelines about seeking immediate medical evaluation to determine if their drugs should be continued.

Despite these precautions, it should be noted that among people with diabetes mellitus, those taking diabetes medications were found to have a lower risk of acute pancreatitis.\textsuperscript{21} In fact, the more medications they were using, the lower the pancreatitis risk.\textsuperscript{21} This potential benefit was seen with a range of diabetes drugs, including metformin, sulfonylureas (eg, glimepiride, glipizide), thiazolidinediones (eg, pioglitazone, rosiglitazone), and α-glucosidase inhibitors (eg, acarbose, miglitol).\textsuperscript{21}

Recently, other diabetes drugs—including exenatide, liraglutide, and sitagliptin—have been linked to pancreatitis, and warnings are included in these drugs’ prescribing information.\textsuperscript{3,4} However, it is not yet clear if the drugs themselves cause inflammation of the pancreas.

**Approaches to Dosing and Routine Use**

Each of the GLP-1 receptor agonists now available is injectable by means of a prefilled, easy-to-use device that looks like a pen. Dosing and administration information for these agents is shown in the Table.

Exenatide is available in 1.2-mL and 2.4-mL prefilled pens. The recommended starting dose of exenatide for patients with T2DM is 5 μg injected subcutaneously twice daily. This initial dose can be administered at any time during the 60-minute period before the morning and evening meals.\textsuperscript{3} After 1 month, the dose of exenatide can be increased to 10 μg twice daily, if needed. The dose should be injected in the thigh, abdomen, or upper arm.

Other recommendations for exenatide administration include the following:\textsuperscript{5}

1. Do not administer the drug after a meal.
2. Administer the doses at least 6 hours apart.
3. Note that the exenatide solution is normally clear and colorless, and therefore it should not be used if the solution is cloudy or discolored or contains particulate matter.
4. Use caution when increasing the dose because of reduced clearance of exenatide (and an increased potential for hypoglycemia) in individuals who are aged 70 years or older and who have moderate renal failure.
5. Continue the current dose of metformin (if the patient is already taking metformin).
6. Consider reducing the dose of sulfonylurea to reduce the risk of hypoglycemia (if the patient is already taking a sulfonylurea).

Liraglutide is available in 3-mL prefilled pens, each containing 18 mg (6 mg/mL) of liraglutide. Each pen can deliver doses of 0.6 mg, 1.2 mg, or 1.8 mg. One pen can deliver a total of 15 doses of 1.2 mg or 10 doses of 1.8 mg. The drug should be injected subcutaneously in the abdomen, thigh, or upper arm at any time of day, and the injection site and timing can be changed without adjusting the dose.\textsuperscript{4}

Treatment with liraglutide should be started at a dose of 0.6 mg daily. After at least 1 week, the dose should be increased to 1.2 mg daily. If glycemic control remains inadequate after 2 weeks of liraglutide at a dose of 1.2 mg daily, the dose can be increased to 1.8 mg daily. In elderly people (ie, aged >70 years) and people with moderate renal failure, caution should be taken when increasing the dose of liraglutide because of reduced clearance of liraglutide (and an increased potential for hypoglycemia).

If the patient taking liraglutide is already taking metformin or a combination of metformin and a thiazolidinedione, the current dose of metformin and glitazone should be continued. If the patient is already taking a sulfonylurea,
the physician should consider reducing the dose of that drug to reduce the risk of hypoglycemia. Although liraglutide can be given at any time of day, independent of meals, it is preferable that the agent be injected at about the same time each day.

The GLP-1 receptor agonists have been shown to have excellent compatibility with all other commonly used treatments for T2DM. Therefore, they are a useful treatment approach for a broad cross section of patients. It is also important to note that, to date, no signs of cardiovascular risk or deleterious effects on bone metabolism have been observed with GLP-1 receptor agonists.

**Consideration of Adverse Effects**

Nausea is the most common acute adverse effect associated with the use of GLP-1 receptor agonists. This effect is more commonly encountered with the shorter-acting exenatide than with the long-acting liraglutide, though nausea is usually transient and mild to moderate with both agents. To mitigate nausea, a number of approaches have been recommended, including counseling patients in advance so that the effect will not come as a surprise, and reassuring them that nausea is transient in most cases.

Ellero et al evaluated the use of antiemetic therapy to reduce nausea and vomiting in 120 healthy adult volunteers who were given 10 μg of exenatide subcutaneously. As expected, the most frequently associated adverse events in these volunteers were nausea (in 39.2% of participants) and vomiting (in 22.5% of participants), both of mild to moderate intensity. However, the incidence of these 2 adverse effects was substantially higher in patients who were not given an antiemetic than in those who were given an antiemetic—61.7% vs 16.7% for nausea, respectively, and 38.3% vs 6.7% for vomiting, respectively.

Patients premedicated with antiemetics showed a higher incidence of somnolence (8.3%) compared to those who were not premedicated (1.7%). Drowsiness is a known adverse event associated with the agents used in the study—metoclopramide and ondansetron.

Finally, pharmacokinetic analysis revealed that plasma exenatide concentrations were similar between groups of participants who did and did not receive antiemetics, indicating the absence of a discernible interaction between the 2 drugs. Therefore, antiemetic therapy is an option to be considered in patients for whom GLP-1 receptor agonists may fill important unmet medical needs, but in whom adverse effects may be a limitation. However, the vast majority of patients who have benefited from the available GLP-1 receptor agonists have done so without the need for additional medications.

**Other Considerations**

The American Diabetes Association (ADA) recommends that, in most patients with T2DM, HbA1c levels be maintained at less than 7.0%, with FPG levels between 70 and 130 mg/dL, and PPG levels less than 180 mg/dL. In some patients—particularly those with diabetes mellitus of short duration, a long life expectancy, and no clinically significant cardiovascular disease—a more stringent HbA1c goal should be considered. The American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel on T2DM recommends an HbA1c level of less than 6.5% as the primary goal. Incretin-based treatments that can avoid hypoglycemia and additional weight gain are important new tools for achieving these goals in patients with T2DM.

Patients with T2DM should be regularly monitored for HbA1c levels, and they should perform self-monitoring of blood glucose levels. Adjustments in therapy should be made as indicated. An HbA1c test is recommended every 3 months in patients whose treatment has recently been changed or in patients who are not meeting their glycemic goals. An HbA1c test should be performed at least twice per year in patients who have stable glycemic control.

To achieve optimum benefit from such agents as GLP-1 receptor agonists, self-monitoring of blood glucose levels should be encouraged and explained, with the understanding that there may be time constraints in a patient’s lifestyle that prevent the patient from performing such self-monitoring on an ideal schedule. Ideally, self-monitoring of blood glucose should be performed on varying days of the week, at different times of the day, after larger meals, and during times when the patient has not eaten for prolonged periods. The major benefit of GLP-1 receptor agonists is reduction of PPG excursions. Therefore, for patients receiving these drugs, a reasonable management approach would be to include more frequent blood sugar measurements after meals (ie, 2 hours after the first bite).

One benefit of GLP-1 receptor agonists is the attenuation of hypoglycemia risk. Indeed, 1 of the most dreaded acute complications associated with treatment for patients with diabetes mellitus is hypoglycemia, which can have important social, economic, job-related, emotional, and psychological consequences for patients. Incretin-based agents are insulin secretagogues that capitalize on a more physiologic sequence of mechanisms than traditional agents. These newer agents enhance insulin secretion and suppress glucagon secretion in a glucose-dependent manner, thereby improving glycemic control while maintaining a low risk of hypoglycemia. It is not unreasonable to think of these agents as “the secretagogues of the 21st century.”
nists promote weight loss by reducing appetite and prolonging gastric emptying time, thereby producing gastric distention and an associated sensation of satiety.\textsuperscript{26}

**Counseling Patients to Optimize Benefits**

Physicians can use a number of approaches to fully empower patients with a comprehensive program of self-management training and T2DM education. Office staff in primary care practices should be aware of general information about diabetes mellitus and resources available on the Internet, which staff should share with patients. Staff should also be trained to teach patients such skills as self-monitoring of blood glucose levels and injection techniques.

Using GLP-1 receptor agonists can be effective in overcoming injection barriers usually encountered when insulin becomes necessary. Furthermore, small group sessions are effective for providing knowledge about diabetes mellitus. Patients who attend these sessions have shown improvements in glucose levels, systolic blood pressure, and body weight, as well as reduced need for medication.\textsuperscript{27}

Primary care providers should establish relationships with certified diabetes educators, registered dieticians, and other specialists in their communities who can help educate patients and their families. These professionals, who are often employees of local hospitals, can come to primary care offices to help facilitate group meetings. If this approach to patient education is not feasible for a practice, patients can be referred to hospital programs in which such services are provided. In addition, as previously indicated, patients can access Web sites to learn about diabetes mellitus. Many of these sites offer free, printable patient education materials that have been developed by such respected organizations as the National Diabetes Education Program (NDEP, http://www.ndep.nih.gov/).

Patient self-management training and education should be ongoing. Clinicians should discuss the disease process and the mechanisms of action of various therapeutic strategies to the fullest extent possible during individual visits. In particular, clinicians should make patients aware that GLP-1 receptor agonists and similar agents are not injections of insulin. After oral or injectable medications are no longer effective in maintaining glucose goals, insulin will still be the most appropriate and physiologically relevant treatment. By the time insulin is needed, the injection hurdle will already have been conquered.

To achieve these goals in the time allotted in most practice settings, it may be necessary to increase the frequency of patient visits, particularly for patients whose T2DM is newly diagnosed, patients with poor glycemic control, or patients with complications.

**Improvements in Education to Ensure Success**

Diabetes education materials have been developed for patients who are at various levels of literacy and numeracy and across various ethnicities and cultures. Organizations that have been especially successful in producing these materials include the NDEP, the ADA (http://www.diabetes.org/), and the American Association of Diabetes Educators (http://www.diabeteseducator.org/). These organizations offer information on a range of topics, from the fundamentals of the pathophysiologic features of diabetes mellitus and disease progression to why specific treatment interventions are recommended. In addition, many books and other printed materials are available for patients.

Patient adherence to lifestyle modifications can be increased by developing a regimen that conforms to the patient’s lifestyle rather than the other way around. With the use of GLP-1 receptor agonists, as with all antidiabetes medications, it is essential that patients be reminded that these agents are designed to be optimally effective when used with consistent programs of healthy nutrition and physical activity.

**Conclusion**

Increasingly, many newer treatment options, guidelines, and algorithms are bringing attention to the appropriate use of incretin-based treatments, such as GLP-1 receptor agonists, for patients with T2DM. These treatments, which are similar to oral agents in effectively controlling blood glucose levels, can address physiologic defects, including α-cell and β-cell dysfunction. These agents are weight neutral or promote weight loss, they have a low risk of hypoglycemia, and they have no known bone or cardiovascular risks.

Glucagon-like peptide-1 receptor agonists are available in injectable form in convenient pen devices and have adverse effect profiles that can be effectively managed with patient education and counseling. As additional forms of these agents become available, it is expected that GLP-1 receptor agonists will play an expanded role in the long-term treatment of patients with T2DM.

**References**


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