Adding glucagon-like peptide-1 receptor agonists to insulin therapy for patients with type 2 diabetes mellitus: why and how?

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Long standing diabetes creates special challenges for the physician and patient. The progressive pathophysiologic nature of diabetes mellitus results in the need for numerous medications to address multiple metabolic defects,\(^1\) with an increasing likelihood of the need for insulin as β-cell function declines.\(^2\) The necessary polypharmacy creates adherence and tolerability challenges for patients.\(^3\)
As diabetes mellitus progresses, the risk of diabetes-related complications increases—including diabetes-related nephropathy—which may influence the choice of therapeutic agents. With nephropathy the excretion of the medication is important, depending on other routes of elimination.4-6

Furthermore, the risk of hypoglycemia is increased with patient age, duration of diabetes mellitus, and impairment in renal function.7 Most osteopathic physicians are relatively comfortable with initiating a single injection of basal insulin as add-on therapy to oral antidiabetic agents when glycosylated hemoglobin (HbA1c) levels are no longer controlled with combination therapy. However, physicians may be less certain about what to do when basal insulin therapy does not maintain treatment goals. Hypoglycemia is a major concern of both physicians and patients and may impact treatment intensification efforts8,9 and patient adherence.10

The use of a single dose of a basal insulin analog (eg, insulin glargine or insulin detemir) is generally indicated if oral antidiabetic therapy has been insufficient to maintain treatment goals.11,12 The selection of long-acting basal insulin may have some benefits over other insulin choices. Long-acting basal insulin analogs are associated with a lower risk of nocturnal hypoglycemia than is neutral protamine Hagedorn (NPH) insulin as a result of their relatively peakless profile.13 Initial recommended dosing of these agents is often 10 units at bedtime, titrated to achieve fasting plasma glucose (FPG) goals of less than 110 mg/dL.11 Titrations can be supervised by the health care team or can be patient driven. Available data show that even insulin-naïve patients can safely and effectively titrate insulin levels.14

One warning about basal insulin titration—be careful not to overbasalize this insulin. Hemoglobin HbA1c levels consist of both FPG and postprandial glucose (PPG) components. The closer a patient is to HbA1c goal (eg, HbA1c of 7% vs 9%), the greater the proportion of hyperglycemia is attributed to postprandial hyperglycemia.15

In the present article, I offer a case report to highlight the need for intensification of therapy in obese patients with long-standing type 2 diabetes mellitus (T2DM) that is no longer being controlled with once-daily injections of basal insulin in addition to oral agents. I also review factors that can impact achievement of treatment goals, challenges in adding medications to therapeutic regimens, and special challenges related to patient education.

**Report of case**

Gloria is a 66-year-old African American woman who is a retired accountant. She presented to her primary osteopathic physician for follow-up treatment for her T2DM. She has a substantial weight problem. At a height of 5 feet 3 inches, she weighs 238 pounds and has a body mass index of 42.2, which places her in the obese classification. She has arthritic changes in her knees and
hips, which, with her excess weight, severely affect her mobility and even threatens the performance of routine activities of daily living. In addition, she has developed severe foot pain that occurs only at rest and affects her ability to sleep. This type of foot pain is often associated with diabetic neuropathy. The patient is generally adherent to her medication regimen, which consists of the following:

— Metformin 2000 mg daily
— Glimepiride 4 mg daily
— Pioglitazone 15 mg daily

Her current laboratory values are as follows:
— HbA1c 7.8%
— FPG 139 mg/dL
— PPG 189 mg/dL
— Serum creatinine 1.2 mg/dL

Discussion: Gloria is young and healthy enough that a HbA1c of <7% should be pursued. She is already on multiple oral antidiabetic medications. Metformin may be nearing the end of its usefulness in this patient, as her renal function is declining. Renal function is dynamic in patients with T2DM and requires close supervision, as do the choices of antidiabetic agents used in the patients. The Table summarizes the metabolism/clearance sites, with dosing adjustments in cases of chronic kidney disease, for commonly used medications in patients with type 2 diabetes mellitus, as adapted from Fonseca.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Metabolism/Clearance Site</th>
<th>Dosing Adjustment/Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glinides</td>
<td>Hepatic</td>
<td>Decreased dose</td>
</tr>
<tr>
<td>GLP-1 agonists</td>
<td></td>
<td></td>
</tr>
<tr>
<td>— Exenatide</td>
<td>Hepatic/renal</td>
<td>Decreased dose</td>
</tr>
<tr>
<td>— Liraglutide</td>
<td>Hepatic/tissue</td>
<td>Caution if prolonged nausea or vomiting</td>
</tr>
<tr>
<td>Insulins</td>
<td>Tissue/renal</td>
<td>Decreased dose</td>
</tr>
<tr>
<td>Metformin</td>
<td>Renal</td>
<td>Discontinue if creatinine¹ 1.4 mg/dL in women,² 1.5 mg/dL in men</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>Hepatic/renal</td>
<td>Glipizide preferred; glyburide has high risk of hypoglycemia; all need decreased dose</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>(eg, pioglitazone)</td>
<td>No dose adjustment</td>
</tr>
</tbody>
</table>

Abbreviation: GLP-1, glucagon-like peptide-1.

Gloria’s physician explained that they would need to adjust her therapy to keep her sugar levels in a safer range.

A basal insulin was added to her regimen. Glargine insulin was started at a dose of 10 units to be administered daily at 10 p.m. The patient was instructed to check her FPG levels each day and to titrate her basal insulin dose based on an average of the last 3 FPG levels. If her FPG 3-day average was greater than 120 mg/dL, she was to increase her insulin glargine by 3-unit increments until an FPG level of 120 mg/dL was achieved.

Insulin glargine titration continued according to schedule until Gloria’s FPG levels stabilized at or near 139 mg/dL. It seemed to Gloria that no matter what she did, adding more basal insulin did not cause her FPG level to change.

**When basal insulin is no longer sufficient**

Basal insulin analogs provide sustained background insulin levels for up to 24 hours in many, but not all patients. Longer-acting insulin analogs currently in development may be able to provide even more consistent and sustained levels in the majority of patients. Basal insulin analogs have a flatter and more prolonged effect than NPH insulin. Increasing the basal insulin dose causes an approximately 0.5% decrease in HbA1c level for each 0.1 U/kg/day increment in insulin dose, up to a threshold of 0.5 U/kg. Beyond this dose, the improvement in HbA1c reduction is less substantial, and the risk of hypoglycemia increases. So at a dose of 0.5 U/kg it may be a good time for osteopathic physicians to reflect on additional treatment options rather than further titration of basal insulin.

Most primary care providers have had to deal with this issue many times. Insulin resistance and β-cell failure are common denominators in patients with T2DM. The balance may tip toward increasing β-cell failure as the pathophysiologic features of T2DM progress and as FPG levels stop responding to basal insulin as glucose control is lost.
during the day with each meal. Increasing basal insulin doses in such cases may not improve glucose control and may lead to increased weight and the risk of hypoglycemia. Insulin resistance, β-cell failure, and over-basalization put the physician at a critical point on the decision tree of diabetes management.

Often the approach to patients not achieving treatment goals with basal insulin analogs is to add 1 or more doses of prandial insulin in the form of a rapid-acting insulin analog (eg, insulin aspart, insulin lispro, or insulin glulisine) or regular human insulin. Although many physicians consider multiple-injection basal-bolus therapy to be the “gold standard,” addition of a single bolus of rapid-acting insulin analog, administered at either breakfast or main mealtime in combination with basal insulin and oral antidiabetic drugs, resulted in a decrease in HbA₁c level from 7.32% to 6.99% \((P < .001)\). Meneghini and colleagues compared 2 intensification strategies for stepwise addition of prandial insulin analogs in patients whose T2DM was inadequately controlled by basal insulin detemir. They found an overall reduction in HbA₁c of 1.2% with stepwise addition of rapid-acting insulin analogs to 1 or more meals, regardless of whether preprandial or postprandial glucose levels were the target of titration efforts.

Limitations of adding prandial insulin to improve glycemic control include its greater complexity for patients to self-titrate, its increased risk of hypoglycemia, and its likelihood of leading to weight gain. Another choice for improving glycemic control would be use of a premixed insulin analog. However that option is probably even less desirable for Gloria because, to be most effective and tolerated, it necessitates strict regularity in mealtimes and meal carbohydrate content. Furthermore, weight gain is more common with premixed insulin supplementation than with the basal bolus insulin regimen previously discussed.

Pramlintide, an amylinomimetic, is approved for use in insulin-treated patients who have either type 1 diabetes mellitus (T1DM) or T2DM and elevated PPG levels. Pramlintide is cosecreted with insulin from pancreatic β-cells and acts centrally to slow gastric emptying, suppress postprandial glucagon secretion, and decrease food intake. These actions complement those of insulin to regulate blood glucose concentrations. Pramlintide is associated with modest beneficial effects on HbA₁c levels when used as adjunctive therapy. Pramlintide is effective at stabilizing blood glucose levels and, once the appropriate dosage is established, it is an effective tool in managing T1DM and T2DM. Pramlintide is also associated with weight loss, which may be attractive, but it carries with it an increased risk of hypoglycemia and it requires an additional injection before every meal. Nausea is a common adverse effect of this medication. Patient education support program may be needed for successful use of this agent. Pramlintide was not considered the best choice for Gloria.

**Basal insulin in combination with incretin-based therapies**

A major challenge to implementing intensive therapy in patients with
T2DM is achieving glycemic control without undue risk of hypoglycemia or weight gain. A new approach would be to consider incretin-based agents, which are not associated with weight gain and which work in a glucose-dependent manner (ie, only in the presence of hyperglycemia). Basal insulin and incretin-based agents are complementary therapies for patients with T2DM—insulin corrects the basic pathophysiologic defect and incretin-based agents improve insulin secretion while decreasing glucagon output.

Combining an incretin-based therapy with insulin is an attractive treatment option for Gloria. This combination has the potential to maximize glycemic control while minimizing the risk of hypoglycemia, to ameliorate the weight gain typical of insulin therapy, and—in patients on established insulin therapy—to decrease insulin dose requirements when used with a glucagon-like peptide-1 (GLP-1) receptor agonist.

**Insulin and DPP-4 inhibitors in combination**

DPP-4 inhibitors are oral agents that work by inhibiting the enzyme that degrades native GLP-1 and thus support maintaining what levels of GLP-1 are still available in patients with T2DM. As such, they are associated with modest reductions in A1c, and are often used as part of combination therapy strategies, but can be used as monotherapy in patients without marked hyperglycemia. These agents, sitagliptin, saxagliptin, and linagliptin are not associated with weight gain or with nausea, and are generally well tolerated.

Of the DPP-4 inhibitors, sitagliptin is currently the only agent approved for use with insulin. Although not paralleling our patient’s case directly, the TRANSITION study examined whether patients using metformin with or without other oral agents and who were not at treatment goals would do better with the addition of sitagliptin with or without a sulfonylurea, or sitagliptin with or without a basal insulin (insulin detemir).22 The combination of once-daily insulin detemir with sitagliptin showed clinically and statistically significant better improvement in glycemic control compared to sitagliptin with or without a sulfonylurea (P<.001).

Saxagliptin also improves glycemic control in patients whose glucose levels are poorly controlled on insulin alone or on insulin and metformin. A placebo-subtracted HbA1c reduction of 0.41% was observed in a study by Barnett et al. 23

When saxagliptin and other DPP-4 inhibitors are used in combination with a sulfonylurea or with insulin, medications known to cause hypoglycemia, the incidence of confirmed hypoglycemia may be increased. Therefore, a lower dose of insulin secretagogue or insulin may be required to minimize the risk of hypoglycemia when used in combination with DPP-4 inhibitors.

Linagliptin has not been studied in combination with insulin therapy.

**Insulin and GLP-1 receptor agonists in combination**

Another option that requires subcutaneous injections—but fewer injections than basal bolus insulin—include the GLP-1 receptor agonists. There are 3 currently available GLP-1 receptor agonists: exenatide twice daily, liraglutide once daily, and exenatide extended release once weekly. Exenatide twice daily and liraglutide once daily are approved for use with basal insulin. The concomitant use of a GLP-1 receptor agonist and insulin may be advantageous for mitigating the weight gain associated with insulin therapy. This is particularly true for obese patients with long-standing T2DM, as is the scenario in
our patient example. Patients using insulin may be already comfortable giving themselves injections, so the addition of another 1 or 2 injections may not be problematic for them.

The use of short-acting exenatide has been studied in patients with T2DM (baseline HbA1c=7.1%-10.5%) who were receiving insulin glargine alone or in combination with metformin and/or pioglitazone. Adding exenatide improved glycemic control (-0.69 placebo-subtracted reduction in A1C) and resulted in weight loss (-2.7 kg different from placebo) without increasing hypoglycemia in these patients, but it increased nausea, diarrhea, and vomiting. Other investigators have explored the addition of the once-daily GLP-1 receptor agonist, liraglutide, to metformin in patients with T2DM, followed by treatment intensification with insulin detemir if HbA1c levels remain at or above 7%. This combination of agents was well tolerated in the majority of patients, resulting in good glycemic control (61% achieved A1C < 7%; mean change -1.7% from baseline A1C 7.7%), sustained weight loss (by 3.5 kg during run-in with lira-glutide, then by .16 kg with insulin detemir and by .95 kg more without detemir) and low hypoglycemia rates. Liraglutide is injected preferably at the same time each day, without regard to mealtimes.

Choosing agents
As previously noted, treatment combinations should include agents that improve glycemic control without increasing the risk of hypoglycemia or weight gain. The incretin-based agents meet these criteria, and—in addition to their efficacy either alone or in combination with other non-insulin agents—they (exenatide and liraglutide) are effective and well tolerated when used in combination with insulin. Addition of incretin-based agents has the potential to spare the patient from prandial (ie, mealtime) injections. GLP-1 receptor agonists are not substitutes for insulin, and they have not been studied in combination with prandial insulin.

If only a modest HbA1c reduction is needed (eg, if HbA1c less than 7.5% with basal insulin), a DPP-4 inhibitor can be added to the patient’s treatment regimen. However, if greater HbA1c reduction is needed or if weight loss is desirable or needed, a GLP-1 receptor agonist can be added. DPP-4 inhibitors are able to cause a less than a 1% decrease in HbA1c level, whereas GLP-1 receptor agonists tend to be more potent and efficacious in achieving goals for patients with higher HbA1c levels.

Dosing considerations
The incidence of hypoglycemia is minimal when DPP-4 inhibitors are added to insulin therapy, so a change in insulin dose is generally not necessary when these agents are combined. Although GLP-1 receptor agonists work via glucose-dependent mechanisms and are associated with a low risk of hypoglycemia when used alone, their hypoglycemia risk is greater when used with insulin or insulin secretagogues (eg, sulfonylureas). Therefore, when GLP-1 receptor agonists are used with insulin, the dose of insulin may need to be reduced. Injections of a GLP-1 receptor agonist may be given at the
same time and in the same general area of the body as insulin injections, but they should not be at the exact same site.

**Patient counseling**

Setting treatment targets with patients when initiating a new medication is always recommended. When adding a GLP-1 receptor agonist, patients can be told that a 1% reduction in HbA1c level is a sign that the drug is working well. Patients can also be informed of the possibility of weight loss with GLP-1 receptor agonists, but it is important to reinforce the need to work with a dietitian or a certified diabetes educator to further improve/maintain healthy dietary habits. Patients should clearly understand that GLP-1 receptor agonists are not the same as insulin and do not replace insulin.

Several tips may improve patient adherence with GLP-1 receptor agonists. For example, physicians can recommend that patients not eat a high-fat meal after injecting a GLP-1 receptor agonist, especially during the early days of therapy to limit gastrointestinal side effects. When prescribing exenatide, physicians should work with patients to determine when they are most likely to eat. The 2 main meals for dosing purposes can then be established. The Figure shows guidelines for improving physician communication with patients with T2DM when adding GLP-1 receptor agonists to insulin therapy.

**Gloria**

When basal insulin fails to control FPG levels, this failure is usually the result of spikes in postprandial sugar levels.14,17 The decision tree of the American Diabetes Association and European Association for the Study of Diabetes12 suggests that prandial insulin can be added in such cases, but there is an alternative that may suit Gloria better.

Gloria is obese and, in most cases, insulin—even analog insulins—will cause weight gain. Recently, GLP-1 receptor agonists have been approved for use with basal insulin.27,28 The longer-acting GLP-1 agents affect both PPG and FPG levels (short-acting exenatide affects primarily PPG), and they are associated with either weight loss or at least much less weight gain than is linked to insulin. Furthermore, GLP-1 agents are associated with much less hypoglycemia than is associated with insulin.29 Thus, for Gloria, adding a GLP-1 receptor agonist may be an appropriate therapy. I made certain to ask Gloria about any personal or family history of thyroid cancer, because GLP-1 receptor agonists are contra-indicated in patients with personal or family histories of medullary thyroid cancers. I also alerted Gloria that these agents have been associated with nausea and vomiting. These gastrointestinal adverse effects generally occur in only a small percentage of patients and abate within a few days to weeks after starting the medication. I informed Gloria that abdominal pain is not common with these agents, but if this adverse event did

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**Figure.** Recommendations for physician communication with patients with type 2 diabetes mellitus when adding glucagon-like peptide-1 receptor agonists to insulin therapy, based on the present case report.
As her physician, I selected liraglutide for Gloria, because its use does not involve dose adjustments for patients with renal insufficiency, and it can be injected once daily without regard to caloric intake. However, I will want to closely monitor her serum creatinine since its 1.2 mg/dL as changing renal function is a real issue to consider in patients with long-term diabetes.

I started Gloria on liraglutide 0.6 mg daily and titrated the dosage to 1.2 mg daily during the next 7 to 10 days. As liraglutide was initiated, I instructed Gloria to suspend her use of glimepiride and to reduce her dose of insulin glargine by 10%, in order to reduce her risk of hypoglycemia. With this treatment regimen, Gloria did not experience nausea, vomiting, or hypoglycemia, and she was pleased that her FPG levels began to decrease within days of starting liraglutide. Within 12 weeks of liraglutide initiation, Gloria’s HbA1c level was at the American Diabetes Association target of 6.9%, and her weight had not increased.

**Future of insulin supplementation**

Although currently available insulin analogs do not represent exact physiologic replacements for endogenous basal bolus insulin, the continued evolution of insulin products and delivery devices is substantially improving the ease of insulin use for patients with T2DM. The refinement in insulin supplementation that has occurred in the last 20 years is dramatic and ongoing. The future holds additional possibilities for improving glycemic control with less hypoglycemia, less variability, and potentially less weight gain and greater patient convenience.

Currently under review by the Food and Drug Administration is insulin degludec, a very long-acting insulin which is in Phase III clinical trials. Insulin degludec forms soluble multi-hexamers upon subcutaneous injection, resulting in a depot from which insulin is continuously and slowly absorbed into circulation to provide an ultralong and steady action profile. This long-acting insulin is administered once daily, but because of its long half-life, it can be considered to be a very “forgiving” insulin—meaning that if a patient forgets to take insulin at the same time each day, some variability in the dosing will not affect blood glucose levels. Compared with insulin glargine, insulin degludec has much less pharmacodynamics variability and, thus, a more predictable glucose-lowering effect from day to day. In studies of patients with either T1DM or T2DM, insulin degludec was associated with less nocturnal hypoglycemia compared to insulin glargine.

Insulin degludec is also being studied as part of combination therapy with insulin aspart (as essentially a bolus boost of rapid-acting insulin). When given once daily in the evening, this combination improved glucose control throughout the day (as measured by
8-point glucose levels) and did so significantly better than insulin glargine for postdinner hyperglycemia.35

Another novel insulin, a PEGylated formulation of insulin lispro is in development but is not far along and has less information available. This PEGylated insulin (LY2605541), which has entered the Phase-II stage of clinical development, has a long duration of action. Compared to insulin glargine, LY2605541 was associated with improved glycemic control and some weight loss in patients with T1DM (ie, those with a mean baseline weight of 183 lb [83 kg]. The baseline weight is only important if we know how much weight loss patients achieved.36 Studies with this agent are currently recruiting participants with T2DM. (Information on this recruitment can be found at http://clinicaltrials.gov/.)

There are also advances in prandial (mealtime) insulin development. A novel ultrarapid-acting insulin in development is associated with less variability among patients than regular human insulin.37 There also is an investigational ultrarapid-acting inhaled insulin that achieves maximum blood concentrations within 15 minutes and has a very short duration of action (~2-3 hours).38

Insulin delivery by inhaler may be possible in the future. Technosphere technology is being investigated as a way to make pulmonary delivery of proteins and peptides possible, essentially by using a dry powder with nanometer-sized particles to carry active drugs so that the drugs rapidly dissolve upon lung contact. In the use of this technology for prandial insulin delivery, less weight gain and fewer hypoglycemic events were observed in combination with a basal insulin, compared to injectable prandial insulin analog added to basal insulin.39 The safety and tolerability profile was similar for both treatment regimens, apart from increased occurrence of cough and changes in pulmonary function in the group receiving inhaled insulin plus insulin glargine.39

Final notes
Advances in pharmaceutical development have greatly increased the therapeutic options available for management of T2DM and the possibilities for combination therapy strategies. Technological developments also are increasing the number of available injectable therapies. Patients should be made aware of these therapies as viable options in their care. Patient education and involvement can improve treatment adherence and reduce the rates of poor outcomes associated with the epidemic of diabetes mellitus.

References

(continued)


