Combining a Glucagon-like Peptide-1 Receptor Agonist with Basal Insulin: The Why and How

**Case Study**
Mary is a 61 year-old female diagnosed with type 2 diabetes mellitus (T2DM) 8 years ago. She was initially managed with the combination of lifestyle modification and metformin. Since that time she was treated with a sulfonylurea, but it was discontinued due to symptomatic hypoglycemia. She was also treated with pioglitazone, but significant fluid retention led to it discontinuation. A year-and-a-half ago, basal insulin was added to her lifestyle and metformin management. She now administers 52 units (0.62 units/kg) once daily at bedtime. Since starting basal insulin, she has experienced 3 episodes of mild hypoglycemia.

Since her diagnosis, Mary’s HbA1c has never been <7.0%; her current HbA1c is 7.9%. Over the past month, her fasting plasma glucose (FPG) has ranged from 103 mg/dL to 136 mg/dL and her postprandial glucose (PPG) from 164 mg/dL to 213 mg/dL. She has gained 2.6 kg since starting basal insulin and her body mass index is now 31 kg/m². Her blood pressure is 134/82 mmHg. She experiences occasional tingling in her feet. Eye examination reveals grade 1 retinopathy.

Current medications are: metformin 1000mg twice daily, basal insulin 52 units once daily at bedtime, and hydrochlorothiazide 25 mg once daily.

Her family physician notes that Mary’s FPG is reasonably well-controlled, yet her HbA1c and PPG remain elevated. He is also concerned about her episodes of hypoglycemia and weight gain and the evidence indicating microvascular damage.

**IMPORTANCE OF POSTPRANDIAL GLUCOSE**
As suggested by this case study, FPG is often the primary target of treatment with glucose-lowering therapy. However, lowering the FPG to the normal range often does not result in achieving a glycated hemoglobin A1c (HbA1c) <7.0%. The reason for this is that PPG also contributes to the HbA1c. Whereas a HbA1c >10.2% is primarily determined by the FPG, a HbA1c <7.3% is primarily determined by the PPG.¹ In fact, the FPG and PPG contribute equally when the HbA1c is in the range of 7.3% to 8.4%.

Beyond its contribution to the HbA1c, increasing 2-hour PPG is associated with an increasing risk of all-cause mortality. The risk increases significantly when the PPG rises above 200 mg/dL.² The risk appears greatest with postprandial hyperglycemia following lunch as shown by a 14-year follow-up of the San Luigi Gonzaga Diabetes Study.³ In this study, the risk of all-cause mortality was similar in magnitude to the risk associated with elevated HbA1c. An increased risk of cardiovascular events was also associated with postprandial hyperglycemia after lunch, as well as breakfast.

**OPTIONS FOR LOWERING POSTPRANDIAL GLUCOSE**
Basal insulin is effective for lowering FPG but has little effect on PPG.⁴,⁵ A three-year study by Holman et al showed that approximately 60% of patients with T2DM achieved HbA1c ≤7.0%
with basal insulin (generally once-daily) in combination with oral agents if taken consistently. The median daily dose of basal insulin was relatively high at 1.0 units/kg and the median rate of a minor (symptoms with blood glucose <56 mg/dL) or major (requiring third-party assistance) hypoglycemic event was 1.7 events/patient/year. However, simply increasing the dose of basal insulin may lead to diminishing returns. In the two-year Treat-to-Target Trial, Riddle et al showed that the reduction in FPG and HbA1c plateaued at a lower daily dose of basal insulin (mean ~0.4 units/kg), while the incidence of hypoglycemia increased with increasing basal insulin dose.

The results of the Holman and Riddle studies suggest that optimizing basal insulin is critical. This involves balancing the efficacy with the safety and tolerability of basal insulin, while considering patient factors such as lifestyle, schedule, capabilities, and willingness to self-monitor blood glucose. The studies also indicate that up to 40% of patients may not achieve glycemic control despite optimized basal insulin. This situation is observed when the HbA1c remains >7.0% despite a normal FPG (as in Mary) and any of the following occur:

- Total basal insulin dose exceeds 0.5 to 1 unit/kg/day
- Severe, nocturnal, or frequent symptomatic hypoglycemia
- Difference between the bedtime and pre-breakfast (BeAM) blood glucose (FPG) >55 mg/dL
- Weight gain

If the BeAM is >55 mg/dL, indicating that the blood glucose decreases significantly overnight, the basal dose is too high. Conversely, if the blood glucose increases significantly overnight, the basal dose is too low. If, however, the bedtime and pre-breakfast (FPG) blood glucose levels are about the same, the dose of basal insulin is correct (assuming no prandial insulin at night).

**INTENSIFYING ONCE-DAILY BASAL INSULIN**

When optimized once-daily basal insulin isn’t adequate to achieve glycemic control, several other options may be considered, including: increasing the frequency of basal insulin to twice-daily, adding prandial insulin (as basal-plus where the bolus is administered before the largest meal of the day, basal-bolus two or three times daily, or premixed biphasic insulin twice-daily), or adding a glucagon-like peptide-1 receptor agonist (GLP-1RA).

**Glucagon-Like Peptide-1 Receptor Agonists**

Following ingestion of food, glucagon-like peptide-1 (GLP-1) is secreted from the L-cells of the jejunum and ileum. GLP-1 stimulates insulin secretion and suppresses glucagon secretion, both in a glucose-dependent manner. In addition, GLP-1 improves insulin sensitivity, slows gastric emptying, and promotes satiety, leading to a reduction of food intake.

Several agonists of the GLP-1 receptor are available, but there are important differences among them. First, exenatide and lixisenatide (investigational) are exendin-4 analogs and albiglutide, dulaglutide, and liraglutide are human GLP-1 analogs. Second, based on the elimination half-lives, exenatide for twice-daily administration and lixisenatide are considered short-acting GLP-1RAs, while the others are considered long-acting GLP-1RAs. Exenatide is given twice-daily,
whereas the remaining GLP-1RAs, including an extended-release form of exenatide, are given once-daily or once-weekly. Beyond dosing, there are other important differences between the short- and long-acting GLP-1RAs (Table 1). Among these are the effects on FPG and PPG. The short-acting GLP-1RAs produce modest reduction of FPG and strong reduction of PPG, while the long-acting GLP-1RAs produce strong reduction of FPG and modest reduction of PPG. The long-acting GLP-1RAs tend to provide significantly greater reduction of HbA1c compared with the short-acting GLP-1RAs. In addition to glycemic effects, a meta-analysis of 25 randomized clinical trials showed that GLP-1RAs produce a mean weight loss of 2.9 kg, mean blood pressure reduction of 3.6/1.4 mmHg, and mean total cholesterol reduction of 3.9 mg/dL.

Gastrointestinal adverse events are common with the GLP-1RAs. The most common is nausea, which occurs in 20% to 50% of patients treated with short-acting GLP-1RAs and attenuates over weeks to many months. By contrast, nausea occurs in 20% to 40% of patients treated with long-acting GLP-1RAs and attenuates over 4 to 8 weeks. Injection site reactions appear to be more common with the long-acting GLP-1RAs.

**Glucagon-Like Peptide-1 Receptor Agonists vs Prandial Insulin**

The efficacy and safety of a GLP-1RA have been compared with prandial insulin, both as add-on therapy to the combination of insulin glargine and metformin. In one study, following a 12-week period to optimize the dose of glargine, patients who did not achieve HbA1c ≤7.0% (N=627) were randomized to exenatide 10-20 mcg twice daily or lispro three times daily; in both cases, the dose of basal insulin was empirically reduced. After 30 weeks of treatment, the reductions in HbA1c were similar (exenatide, -1.13% vs lispro, -1.10%) (Table 2). As expected, the change in FPG was significantly greater with exenatide than insulin lispro (-8.3 vs 3.2 mg/dL; \( P=.002 \)). Changes in PPG were similar except after lunch where the reduction with exenatide was less than with insulin lispro (-39.2 vs -56.0 mg/dL; \( P<.001 \)).

The long-acting GLP-1RA albiglutide also has been compared with prandial insulin, both as add-on therapy to the combination of insulin glargine and oral agents (N=563). Using a study design similar to the exenatide vs lispro study, the reductions in HbA1c were similar at 26 weeks (albiglutide, -0.82% vs -0.66%). The reductions in FPG also were similar (-17.8 vs -12.8). Albiglutide, given once-weekly, resulted in weight loss and lower risk of hypoglycemia than insulin lispro given three times daily.

**Glucagon-Like Peptide Receptor Agonist vs Glucagon-Like Peptide Receptor Agonist**

Lixisenatide (investigational) has been compared with liraglutide, both once-daily in combination with insulin glargine after optimized titration. After 8 weeks, both lixisenatide 20 mcg and liraglutide 1.2 and 1.8 mg once daily improved glycemic control to an HbA1c of 6.1% to 6.2%. Lixisenatide demonstrated a significantly greater reduction of PPG after a standardized breakfast than either dose of liraglutide, possibly due to a greater delay in gastric emptying with lixisenatide. Reductions in body weight and daily insulin dose were similar in the lixisenatide and liraglutide 1.8 mg groups. Symptomatic hypoglycemia was higher with lixisenatide (lixisenatide, 29.2%; liraglutide 1.2 mg, 19.1%; liraglutide 1.8 mg, 21.3%), while
gastrointestinal adverse events were more common with liraglutide (lixisenatide, 35.4%; liraglutide 1.2 mg, 44.7%; liraglutide 1.8 mg, 46.8%).

**BASAL INSULIN AS ADD-ON THERAPY TO A GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONIST**

The addition of basal insulin to a GLP-1RA has been investigated in patients not achieving glycemic control with metformin with or without a sulfonylurea.\(^{25}\) Patients underwent a 12-week run-in period in which the sulfonylurea was discontinued and liraglutide was initiated and titrated to 1.8 mg once daily. If the HbA1c was ≥7.0%, patients were randomized to continue treatment or be treated with the addition of insulin detemir in the evening, with the dose titrated to achieve FPG 74 to 108 mg/dL. After 26 weeks, the HbA1c decreased further by 0.5% with the addition of insulin detemir versus an increase of 0.2% without the addition of insulin detemir (\(P<.0001\)). Moreover, the reduction in the PPG following breakfast, lunch, and dinner was significantly greater with the addition of insulin detemir. During the run-in period, the mean weight decreased by 3.5 kg. Following randomization, weight decreased by 0.16 kg with the addition of insulin detemir or 0.95 kg without insulin detemir. No major hypoglycemia occurred and the rates of minor hypoglycemia were 0.286 and 0.029 events/patient/year, respectively.

**META-ANALYSIS: A GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONIST IN COMBINATION WITH BASAL INSULIN**

A meta-analysis of 14 observational/clinical practice studies and five clinical trials assessed the outcomes of adding a GLP-1RA to basal insulin.\(^{26}\) The analysis involved approximately 5000 patients treated over 5 to 48 months. The most common result across all studies was that the combination of a GLP-1RA and basal insulin improved glycemic control without weight gain or an increased risk of hypoglycemia. Many studies also reported weight loss and a reduction in the total daily insulin dose when a GLP-1RA was added to basal insulin.

**BASAL INSULIN/GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONIST COMBINATION PRODUCTS**

Two products that combine a basal insulin with a GLP-1RA are under investigation in the United States. One combination, insulin degludec and liraglutide (IDegLira), was investigated in a 26-week, randomized, double-blind study involving 413 patients with T2DM. Patients had an HbA1c of 7.5% to 10.0% despite basal insulin and metformin with or without sulfonylurea/meglitinides. The HbA1c decreased 1.9% in patients treated with IDegLira compared with 0.9% in patients treated with insulin degludec (\(P<.0001\)). Mean weight decreased 2.7 kg with IDegLira but did not change with insulin degludec (\(P<.0001\)). The incidence of hypoglycemia was similar (24% vs 25%, respectively).

The other combination, insulin glargine 100 units/mL and lixisenatide (iGlarLixi), has been investigated in two 30-week trials. In the first, iGlarLixi provided superior HbA1c reduction compared with lixisenatide or insulin glargine 100 units/mL, all in combination with metformin in patients who did not achieve glycemic control with metformin with or without oral agents.\(^{27}\) In the second, iGlarLixi provided superior HbA1c reduction compared with insulin glargine 100 units/mL with or without oral agents.\(^{28}\) In both studies, the safety profiles were similar among treatment groups.
RECOMMENDATIONS FOR GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONIST USE IN COMBINATION WITH BASAL INSULIN

Based upon the results of clinical trials, the use of a GLP-1RA in combination with basal insulin in patients who do not reach their glycemic target with two or three glucose-lowering medications is a reasonable option. If the GLP-1RA is added in a patient already taking a sulfonylurea, consideration should be given to discontinuing or reducing the dose of the sulfonylurea. If the GLP-1RA is added in a patient already taking basal insulin and the HbA1c is ≤7.5%, consideration should be given to reducing the basal insulin dose 10% to 20%. Thereafter, the insulin dose can be adjusted based on self-monitoring of blood glucose. Monitoring for hypoglycemia is important during all changes in treatment.

Currently, albiglutide, exenatide twice-daily, and liraglutide are approved by the US Food and Drug Administration for use in combination with basal insulin. Dulaglutide is approved for use in combination with prandial insulin. Exenatide once-weekly has not been approved for use in combination with basal or prandial insulin.
Table 1. Pharmacodynamics of GLP-1 Receptor Agonists.\textsuperscript{13}

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<tr>
<th>Effects</th>
<th>Short-Acting</th>
<th>Long-Acting</th>
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<tbody>
<tr>
<td>Fasting blood glucose</td>
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<td>Strong reduction</td>
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<tr>
<td>Postprandial blood glucose</td>
<td>Strong reduction</td>
<td>Modest reduction</td>
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<tr>
<td>Fasting insulin secretion</td>
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<td>Strong stimulation</td>
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<tr>
<td>Glucagon secretion</td>
<td>Reduction</td>
<td>Reduction</td>
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<td>Gastric emptying rate</td>
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<td>Body weight</td>
<td>1-5 kg Reduction</td>
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Table 2. Prandial insulin vs GLP-1RA in combination with optimized insulin plus metformin.\textsuperscript{24}

<table>
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<th>Study Results: Summary</th>
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<tbody>
<tr>
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Reference List


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