Achieving Glycemic Control: When Optimized Basal Insulin Isn’t Adequate

Case Study
Alison is a 48 year-old female diagnosed with type 2 diabetes mellitus (T2DM) 8½ years ago. She changed primary care physicians about 10 months ago. At that time, she was taking metformin in combination with a sulfonylurea. Her HbA₁C was 8.6%. Her glucose log showed that her fasting blood glucose ranged from 138 to 164 mg/dL; postprandial blood glucose was not monitored. Basal insulin once daily with dinner was added and the sulfonylurea discontinued.

Alison has titrated her dose of basal insulin to achieve a fasting blood glucose <130 mg/dL. She is now administering 58 units (0.56 units/kg) with dinner. Her HbA₁C is 7.6%. Her fasting blood glucose over the past week has ranged from 92 to 133 mg/dL and her bedtime glucose from 162 to 190 mg/dL. She has experienced 2 episodes of symptomatic hypoglycemia during the past 3 months, the last episode causing her to fall. She has gained 2.4 kg (body mass index increase of 1.4 kg/m²) since beginning insulin.

Patients with diabetes have both basal and prandial hyperglycemia. Since hyperglycemia is largely determined by the fasting blood glucose above a glycated hemoglobin (HbA₁C) of 8.5%, the fasting blood glucose is the primary initial target in most persons with type 2 diabetes mellitus. Among all options for lowering the blood glucose, basal insulin is the most effective in lowering the fasting blood glucose level. Among the basal insulins, the insulin analogs are preferred over neutral protamine Hagedorn (NPH) insulin since the basal insulin analogs are less likely to cause hypoglycemia.

In addition to a low risk of hypoglycemia, desirable clinical effects of basal insulin include a duration of action > 24 hours; peakless blood level, particularly with doses < 0.5 units/kg; effective reduction of hepatic glucose production and lipogenesis; and primarily targets the fasting blood glucose.

Optimizing basal insulin is typically a balance between efficacy, safety/tolerability, and consideration of patient factors such as lifestyle, schedule, interests, and capabilities. If the dose of basal insulin is correct, the bedtime blood glucose should be about the same as the next morning’s fasting blood glucose (provided prandial insulin is not used at dinnertime and there is no additional caloric intake in the evening). Most patients with type 2 diabetes mellitus can achieve long-term glycemic control (HbA₁C ≤7%) with basal insulin in combination with oral agents if taken consistently; however, approximately 40% do not. In these cases, residual postprandial hyperglycemia is the cause. This may be a concern since hyperglycemic spikes following meals are thought to be associated with increased cardiovascular risk due to the induction of oxidative stress, endothelial dysfunction, and inflammatory reactions.

Indications that optimized basal insulin may not be enough to achieve glycemic control include a HbA₁C >7% despite a fasting blood glucose 80 to 130 mg/dL and one or more of the following:
• Total dose of basal insulin > 0.5 to 1 unit/kg/day\textsuperscript{4,5}
• Difference between the bedtime and fasting blood glucose >55 mg/dL\textsuperscript{6}
• Severe, nocturnal, or frequent symptomatic hypoglycemia
• Weight gain

The total daily dose of basal insulin at which safety/tolerability begins to outweigh efficacy likely varies among patients. Dosing recommendations by the American Diabetes Association/European Association for the Study of Diabetes suggest the tipping point between efficacy and safety/tolerability may occur with a total daily dose of basal insulin between 0.5 and 1 unit/kg.\textsuperscript{4,5} However, a lower maximum dose is suggested by the Treat-to-Target Trial by Riddle et al.\textsuperscript{7} In this 24-week study of patients with type 2 diabetes mellitus, the reduction in fasting blood glucose began to plateau at a total daily dose of basal insulin of approximately 0.30 to 0.35 units/kg/day. Higher doses of basal insulin resulted in a small reduction in the fasting blood glucose at the expense of a rising incidence of hypoglycemia.

Case Study (cont)
Alison’s primary care physician discusses the need for additional glucose-lowering therapy that targets postprandial glucose. The options include: rapid-/short-acting insulin; a glucagon-like peptide-1 receptor agonist (GLP-1RA), a dipeptidyl peptidase-4 inhibitor (DPP-4i), and a sodium glucose cotransporter-2 inhibitor (SGLT-2i).

Numerous factors are to be considered in selecting therapy to lower postprandial glucose (PPG). These include medication factors such as the magnitude and durability of the glycemic response; mechanism of action that is complementary to other medications being taken; requirement for functioning pancreatic β-cells; adverse events; warnings and contraindications; and out-of-pocket cost. Patient factors include body weight; regularity and quality of meals; variations in physical activity and work schedule; hypoglycemia awareness and tolerance; and adherence.

Traditionally, a rapid- or short-acting insulin has been used to reduce postprandial glucose (PPG). While effective in lowering PPG, prandial insulin increases the risk of hypoglycemia, contributes to weight gain, and must be administered at mealtime. A DPP-4i or SGLT-2i are reasonable alternatives, although they are less effective in lowering PPG than prandial insulin or a GLP-1RA, particularly a short-acting GLP-1RA such as exenatide twice-daily.\textsuperscript{2,5,8} Below are further considerations for therapy targeting PPG.\textsuperscript{5}

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<th>Alison...</th>
<th>Rapid-/Short-acting Insulin</th>
<th>GLP-1RA</th>
<th>DPP-4i</th>
<th>SGLT-2i</th>
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<td>is concerned about:</td>
<td>• Further hypoglycemia • Further weight gain</td>
<td>• Additional injection • Transient N/V • ?Acute pancreatitis • C-cell hyperplasia/medullary</td>
<td>• Immune-mediated dermatologic effects</td>
<td>• Genital yeast infections • Polyuria</td>
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<td>• Potential for multiple daily injections</td>
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<td>• Heart failure hospitalizations</td>
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**Basal Insulin in Combination with GLP-1RA**

The combination of basal insulin and a GLP-1RA is a recommended option in recent management guidelines for type 2 diabetes mellitus.²⁵,⁸ This recommendation is supported by an increasing body of evidence.

Exenatide 10 mcg twice daily has been compared with placebo as add-on therapy to insulin glargine plus oral agents in patients with T2DM and HbA₁C 7.1-10.5%.⁹ Patients were receiving insulin glargine alone or in combination with metformin or pioglitazone or both. After 30 weeks, the HbA₁C decreased by 1.74% with exenatide and 1.04% with placebo (P<.001). The self-monitored blood glucose levels were lower at all non-fasting times in the exenatide group than in the placebo group (P<.001), as were morning and evening PPG excursions. The number of hypoglycemic events per patient per year did not differ significantly between the exenatide and placebo groups. Major hypoglycemia was experienced by 1 patient in the placebo group. Weight decreased by 1.8 kg with exenatide and increased 1.0 kg with placebo. Average increases in the daily dose of insulin glargine were 13 units with exenatide and 20 units with placebo.

Exenatide has been compared with insulin lispro as add-on therapy to insulin glargine plus metformin in patients with T2DM.¹⁰ Patients underwent optimization of the insulin glargine dose over 12 weeks to achieve a fasting blood glucose ≤100 mg/dL. Those who didn’t achieve HbA₁C ≤7.0% were randomized to exenatide 10 mcg twice daily or insulin lispro three times daily for 30 weeks; the dose of basal insulin was adjusted downward. At study end, HbA₁C decreased 1.13% with exenatide and 1.10% with lispro. The end-of-treatment fasting blood glucose was significantly lower with exenatide than lispro (117 vs 130 mg/dL; P=.002). Postprandial glucose excursions were similar except for the midday meal when exenatide was not administered. The incidence of hypoglycemia was greater for lispro for minor (41 vs 30% for exenatide) and confirmed nocturnal (34 vs 15% for exenatide) hypoglycemia. Two exenatide and 7 lispro patients had at least 1 major hypoglycemic episode. The incidence of nocturnal hypoglycemia was similar for exenatide and lispro (25 vs 27%, respectively). Weight decreased
with exenatide and increased with lispro (-2.5 vs 2.1 kg; \( P < .001 \)). The end-of-study dose of glargine was lower in the lispro group. Treatment satisfaction was greater in the exenatide group.

The results of these two studies are generally consistent with the results of a systematic literature review of randomized controlled studies of basal insulin in combination with a GLP-1RA.\(^1\) The most common finding across all types of studies included in the systematic review was that the combination of basal insulin and GLP-1RA improved glycemic control without weight gain or an increased risk of hypoglycemia. Many studies reported weight loss and a reduction in the total daily dose of basal insulin. The adverse event profile was similar to that reported with GLP-1RAs as monotherapy or in combination with oral agents with gastrointestinal events being the most common.

**Summary**

Optimized basal insulin may not be enough to achieve glycemic control due to residual postprandial hyperglycemia. Postprandial hyperglycemia is an important treatment consideration as it is associated with increased cardiovascular risk. Rapid-/short-acting insulin has been the standard to lower postprandial glucose; however, recent recommendations indicate a GLP-1RA is an effective alternative. Compared to thrice-daily rapid-acting insulin, the addition of the short-acting GLP-1RA exenatide twice-daily to basal insulin provides similar or better glycemic control, less nocturnal hypoglycemia, weight loss (vs weight gain), and greater treatment satisfaction.
Reference List


