

Case Study: Use of GLP-1 Receptor Agonist in a Patient on Intensive Insulin Therapy

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Current treatment of type 2 diabetes begins with diet and lifestyle modifications accompanied by use of oral antihyperglycemic medications. Despite multiple therapeutic options for people with type 2 diabetes, the disorder continues to progress, resulting in the gradual deterioration of glycemic control over time (1). This is the result of insulin resistance and progressive decline in β -cell function, combined with increased hepatic glucose output as a result of glucagon dysregulation (2). These factors lead to elevations in both fasting and prandial glucose levels.

It is well known that poor glycemic control is associated with increased risk of microvascular and macrovascular complications. Ultimately, basal insulin, premixed insulin, and/or prandial insulin are added to the treatment regimen (3). The U.K. Prospective Diabetes Study and its follow-up found that patients with uncontrolled type 2 diabetes receiving intensive insulin therapy had significantly lower risks of microvascular and macrovascular complications, as well as lowered mortality rates compared to diabetes patients on standard therapy (1,4). However, intensive insulin therapy is associated with weight gain and hypoglycemia (1).

A plethora of other treatment options are available for diabetes patients, many of which are either weight neutral or promote weight loss. The downside of having these

additional treatment options is that the wide range of choices may present a challenge to prescribers when determining the optimal therapeutic regimen. In making these decisions, health care providers should consider patients' disease progression state, comorbidities, and concomitant treatments (5).

GLP-1 receptor agonists are one of the newer drug classes to appear on the market. These agents have been proven to be effective without increased risk of hypoglycemia or weight gain (6,7). They are ideal for patients who have had episodes of hypoglycemia on large insulin doses and for obese patients who could benefit from the modest weight loss associated with their use. These agents can also be considered for patients who are failing to achieve adequate glycemic control on one or more oral medications.

Currently, patients on GLP-1 receptor agonists are either not concurrently taking insulin or are only taking basal insulin (insulin glargine or insulin detemir) per U.S. Food and Drug Administration (FDA) guidelines. Several observational studies have shown that the combination of basal insulin and a GLP-1 receptor agonist results in improvements in postprandial glucose, excess weight, and A1C (a component of hemoglobin in which glucose binds), with no substantial increase in hypoglycemia (8–13). These studies also found that immediate-release exenatide had a more significant impact on postpran-

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dial glucose levels than liraglutide, whereas liraglutide preferentially targeted fasting glucose levels while also having a lowering effect on postprandial glucose. There have been no randomized, controlled trials of the use of a GLP-1 receptor agonist in conjunction with premixed or prandial insulin, and such use is not incorporated in the new American Diabetes Association recommendations (2).

United Kingdom specialist clinicians are exploring the use of GLP-1 receptor agonists in combination with bolus and basal insulin for obese type 2 diabetes patients with poor glycemic control (14). However, there is not yet enough evidence regarding how to initiate this combination in patients or what outcomes can be expected. The following case study provides a successful account of the use of liraglutide and insulin aspart protamine/insulin aspart 70/30 mix in an obese patient with poorly controlled type 2 diabetes.

Case Presentation

L.T. is a 27-year-old woman with type 2 diabetes who presented to the Howard University Hospital diabetes clinic for the first time in June 2008. She was diagnosed with type 2 diabetes in June 1995, at the age of 9 years, by her primary care physician. (Type 1 diabetes was ruled out by negative anti-islet antibody test results.) L.T. has a family history of diabetes, high blood pressure, and elevated cholesterol. She is a nonsmoker with no children and works at a fast-food chain.

She was taking NPH 20 units in the morning and 15 units in the evening and regular insulin 25 units in the morning and 15 units in the evening for her diabetes. She was also taking atorvastatin 10 mg daily for hypercholesterolemia (elevated LDL cholesterol, low HDL cholesterol, and elevated triglycerides), warfarin 7.5 mg daily for deep venous thrombosis, ergocalciferol 50,000 units for vitamin D deficiency, and lisinopril/

hydrochlorothiazide 20/25 mg for high blood pressure. Her compliance with these medications, and with her insulin regimen, was poor. She reported having periods during which she takes her medications as prescribed and other times when she does not. As a result, her blood pressure and cholesterol cycle from being controlled to uncontrolled. L.T. has never been compliant with keeping scheduled appointments or checking her blood glucose. She reported that she had not been checking during the 3 months before this initial visit because she had run out of test strips.

L.T.'s initial complaints were visual disturbances, burning and tingling in her feet and legs, alterations in appetite, weight gain, edema, nausea, and irritability. She also felt depressed because she believed that diabetes-related stress had had a negative effect on her family life, social activities, finances, sports and exercise activities, school and work performance, and sexual relations. Her A1C was 8.9%.

Her biggest concern was her weight. At her initial visit, she weighed 265 lb. She stated that her most comfortable weight is 190 lb and that she had experienced an unplanned weight gain of 35 lb in the past 3 months. She was given a meal plan in the past but said she did not adhere to it. She reported that the stress of her disease causes her to overeat, although she does exercise regularly, and her exercise program includes walking. Overall, however, she rates her personal health as poor.

In the years following her initial presentation to the clinic, L.T. missed several appointments and was very inconsistent with her insulin regimen. Her A1C climbed to a peak of 11.1%. She also developed albuminuria. Her insulin doses were intensified in an attempt to gain control of her diabetes, but the increased dosage resulted in only a slight improvement in her diabetes. On a regimen of insulin glargine 40 units daily and insulin aspart 15 units with meals, her A1C

improved slightly to 10.8%, but her weight increased by 12 lb to a total of 297 lb.

The medical team eventually decided to change L.T.'s regimen to insulin aspart 70/30 mix 45 units twice daily, and, a month later, liraglutide was added (Table 1). The goal of this combination was to lower the number of daily injections, lower the total daily insulin dose, encourage weight loss, and improve glycemic control. Liraglutide was started at 0.6 mg daily subcutaneously for 1 week and then increased to 1.2 mg daily.

At the follow-up visit 1 month later, LT denied any side effects or adverse reactions with liraglutide therapy and was pleased that she had lost 2 lb. She also reported checking her blood glucose more often while on liraglutide and having lower readings than when she was on insulin therapy alone.

Three months later, L.T.'s A1C had greatly improved to 7.6%. She admitted to having some low readings but said they were asymptomatic and did not require medical attention. In total, she had 34 hypoglycemic readings (blood glucose <70 mg/dL) and some as low as 19 mg/dL, but none required hospitalization. More than 95% of the hypoglycemic readings were >50 mg/dL and were readily treated with either three 5-mg glucose tablets, 4 oz of fruit juice or nondiet soda, or 8 oz of skim milk. Because of concern about continued hypoglycemia, her insulin dose was decreased to 30 units twice daily.

At follow-up 2 months later, L.T.'s average glucose readings were 133 mg/dL. While taking liraglutide, she had lost 20 lb, and her BMI had decreased by 3 kg/m² with no changes in diet or activity level. None of her other diabetes medications were adjusted during this 6-month period, and she did not use over-the-counter medicines or dietary supplements.

Discussion

In individuals with diabetes, plasma glucagon concentrations are inappro-

TABLE 1. L.T.'s Diabetes Medication Changes Over Time

Reference Date	Medication Change	A1C (%) at Time of Change
First day at clinic (3 years before starting liraglutide)	NPH insulin: 20 units at breakfast, 15 units at dinner Regular insulin: 25 units at breakfast, 15 units at dinner	8.9
14 months before starting liraglutide	Insulin aspart 70/30 mix: 40 units at breakfast, 30 units at dinner	9.7
13 months before starting liraglutide	Insulin aspart 70/30 mix: 35 units twice daily	11.1
10 months before starting liraglutide	Insulin glargine: 40 units at bedtime Insulin aspart: 15 units with meals	10.8
6 months before starting liraglutide	Insulin glargine: 45 units at bedtime Insulin aspart: 15 units with meals	12.2
1 month before starting liraglutide	Insulin aspart 70/30 mix: 45 units twice daily	11.4
Date liraglutide was added	Insulin aspart 70/30 mix: 45 units twice daily Liraglutide: 1.2 mg	11.4
3 months after starting liraglutide	Insulin aspart 70/30 mix: 35 units twice daily Liraglutide: 1.8 mg	7.6
6 months after starting liraglutide	Insulin aspart 70/30 mix: 30 units twice daily Liraglutide: 1.8 mg	7.7

privately elevated and α -cell suppression by hyperglycemia is blunted. This results in a greater rate of hepatic glucose production in the fasting state and attenuated reduction after meals (15). Therefore, medications such as the GLP-1 receptor agonists and DPP-4 inhibitors are unique and exciting options because they target the glucagon pathway.

Currently available GLP-1 receptor agonists include exenatide and liraglutide. Additional GLP-1 receptor agonists in clinical development include once-daily lixisenatide and twice-weekly albiglutide and dulaglutide (16). These agents are incretin mimetics; they bind to the GLP-1 receptor, resulting in the stimulation of insulin secretion in a glucose-dependent manner. GLP-1 receptor agonists also normalize hypersecretion of glucagon during the postprandial state. There is very low risk of hypoglycemia with these agents when used alone because the glucose-mediated secretagogue effect of GLP-1 receptor agonist therapy fades as glucose levels fall (unlike with sulfonylureas). When used with

other glucose-lowering agents such as insulin, the risk for hypoglycemia increases with these agents. Other effects of GLP-1 receptor agonists include slowing the rate of gastric emptying and improving satiety, which likely contribute to improvements in postprandial hyperglycemia, fasting glucose, and A1C (17).

As mentioned earlier, GLP-1 receptor agonists are dosed differently depending on the drug and formulation. Immediate-release exenatide is dosed twice daily, whereas extended-release exenatide is dosed once weekly; liraglutide is dosed once daily. They are all delivered subcutaneously and are easier than insulin to administer. In comparison to insulin, the volume injected is very small, syringes and vials are not needed, and doses do not vary with the size of meals or activity.

The main side effect of GLP-1 receptor agonists is mild to moderate nausea, which diminishes with prolonged therapy. There have also been documented reports of animal studies showing an association of extended-release exenatide and liraglutide with

formation of C-cell tumors in the thyroid gland. There have been no cases in humans of these agents causing cancer; however, C-cell formation is listed as a warning in the package insert. There is also a risk of pancreatitis with these agents. Practitioners should monitor patients' serum amylase and lipase when patients complain of pancreatitis symptoms while on these agents. It should be noted that DPP-4 inhibitors such as sitagliptan also carry the increased risk of pancreatitis. Another possible disadvantage to GLP-1 receptor agonists is that patients who have burned out their β -cells may not respond as well to therapy with these agents.

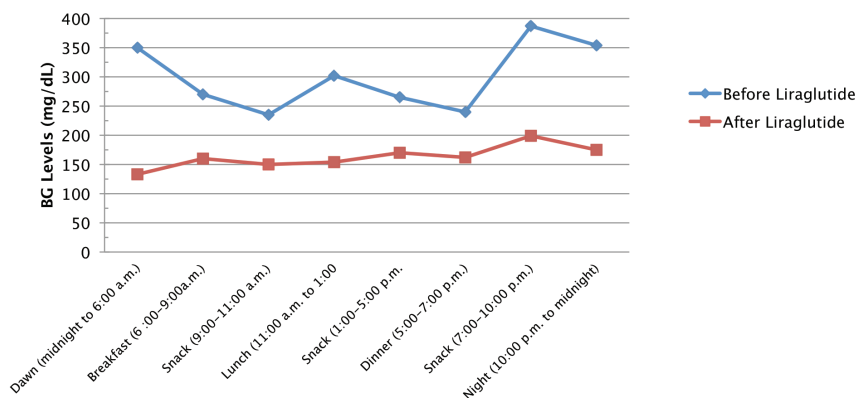
The major advantages with this drug class are the low incidence of hypoglycemia (compared to insulin and secretagogues), potential weight loss, and less stringent contraindications based on clinical or laboratory assessments of organ function before initiation of therapy (as is needed with metformin and thiazolidinediones) (17). No dosage adjustment is necessary for hepatic impairment for any of the available GLP-1 receptor agonists.

With liraglutide, no dose adjustment is required for renal impairment, and the exenatide formulations can be used in mild to moderate chronic kidney disease (although exenatide is not recommended if creatinine clearance is <30 mL/min). Also, studies have found that GLP-1 receptor agonist therapy shows promise in preserving and improving markers of β -cell function and favorable changes in risk factors and markers for cardiovascular disease (18).

L.T. presented with uncontrolled type 2 diabetes and complex comorbidities, all of which required treatment. She tried several different insulin regimens, none of which resulted in optimal blood glucose control. She had many additional factors exacerbating her diabetes diagnosis, including poor diet, morbid obesity, sedentary lifestyle, noncompliance with medications, and depression.

Despite repeated reminders to check her blood glucose at home, L.T. did not do so consistently, which resulted in more difficult decisions when adjusting her medications. For example, despite being encouraged to check her blood glucose at least three times daily (before her insulin injections and before bedtime), over a period from January to June 2011, she recorded only 72 readings. L.T.'s average blood glucose reading during this time was 295 mg/dL, with a minimum of 58 mg/dL and a maximum of 601 mg/dL. Forty-eight of the readings were >200 mg/dL. Only 28% of her readings were within her target range.

After multiple approaches failed to control L.T.'s blood glucose, she was finally given liraglutide, along with her aspart 70/30 mix, and this regimen yielded the best response. Her A1C dropped from 10.8 to 7.6%. Along with her improved diabetes control, she also reported performing more self-monitoring of blood glucose. In fact, from 30 July to 30 December 2011, she tested her blood glucose 193 times (121% more



■ FIGURE 1. L.T.'s blood glucose readings 6 months before and 6 months after adding liraglutide.

often than in the previous 6-month period). She averaged 1.25 readings per day compared to 0.47 readings per day before starting liraglutide. Results in her target range increased from 28 to 44%. Her mean blood glucose during this period was 166 mg/dL, which is lower than it had been during the previous 6 months (Figure 1). However, she did have more hypoglycemic readings on liraglutide, although none resulted in a hospital visit. Determining a medication's potential to cause hypoglycemia is an important consideration when altering a patient's diabetes pharmacotherapy regimen.

Weight loss was a great benefit of liraglutide therapy for this patient. L.T.'s main concern with her insulin regimen was its associated weight gain. A few months after initiation of liraglutide, the dose of the insulin was decreased, and an almost immediate weight loss was observed. During the course of her liraglutide treatment, she lost 20 lb, and her BMI decreased from 55 to 52 kg/m². Similarly, in the second phase of the SCALE (Satiety and Clinical Adiposity—Liraglutide Evidence in Non-Diabetic and Diabetic Subjects) trial (19), the proportions of people achieving a weight loss $\geq 5\%$ or $\geq 10\%$ were 50% and 22%, respectively, for liraglutide 3 mg; 35% and 13%, respectively, for liraglutide 1.8 mg; and 13%

and 4%, respectively, for placebo. It should be noted, however, that during the 12-week follow-up period after treatment discontinuation, both liraglutide treatment groups experienced a moderate weight regain. In general, most patients will lose a moderate amount of weight (0–10 lb) in the first few months of therapy and then plateau; in rare instances, patients can lose significant amounts of weight while taking liraglutide.

Other observational studies involving the addition of a GLP-1 receptor agonist to prandial insulin have been reported. Yoon et al. (20) observed 188 patients taking a GLP-1 receptor agonist and insulin over a 27-month period and found that the longer patients used this combination, the more their A1C decreased. Mean percentage-point decreases in A1C were -0.66 at 0–6 months, -0.55 at 6–12 months, -0.54 at 12–18 months, and -0.54 at 18–27 months. This study also reported that weight and total daily dose of insulin (mostly prandial insulin) decreased the longer patients were on this combination, with a mean weight loss of 5.5 kg. Sheffield et al. (21) performed a similar study with immediate-release exenatide and insulin in 134 patients for 1 year. The study found that exenatide use resulted in a significant 0.87 percentage-point reduction in A1C, as well as discontinuation

of premeal insulin use in 45% of patients, a 9-unit reduction in mean premeal insulin doses, a decrease in the median number of daily insulin injections, and a mean weight loss of 5.2 kg. Viswanathan et al. (22) also reported data on 38 patients who completed 26 weeks of treatment with immediate-release exenatide and insulin. They found that mean A1C decreased by 0.6 ± 0.21 percentage points, insulin requirements decreased for mixed and rapid-acting insulins, and mean body weight decreased by 6.46 ± 0.8 kg. An additional study by Balena et al. (18) found that, over a 12-month period, adding immediate-release exenatide to an insulin regimen resulted in a mean A1C reduction of 0.51 percentage points, weight loss of 5.8 kg, insulin dose reduction of 42 units/day, and cessation of insulin use in 16.6% of patients. A study in type 1 diabetes patients by Kielgast et al. (23) reported that the use of combination therapy with liraglutide and insulin reduced the insulin requirement from 0.50 ± 0.06 to 0.31 ± 0.08 units/kg/day in C-peptide-positive patients and from 0.72 ± 0.08 to 0.59 ± 0.06 units/kg/day in C-peptide-negative patients while maintaining or improving glycemic control.

GLP-1 receptor agonists also have been shown to produce slight reductions in blood pressure for patients with hypertension (reductions of 1–5 mmHg in systolic and diastolic blood pressure) (24). L.T.'s blood pressure remained controlled (<140/90 mmHg) while taking liraglutide and her blood pressure medications (lisinopril 20 mg and hydrochlorothiazide 25 mg). Liraglutide also has been found to improve the lipid panel of patients with dyslipidemia (25). L.T.'s lipid panel has not been ordered since she started liraglutide.

Because of the progressive nature of type 2 diabetes, many patients will require multiple therapeutic strategies to maintain glycemic targets (26). Although control can be

accomplished with intensive insulin regimens, these can result in a higher risk for hypoglycemia and weight gain, which is burdensome for patients (27–29). Adding a GLP-1 receptor agonist is a potential solution to this challenge because it complements the activity of insulin and may lower the daily insulin dose required to maintain glycemic control.

Conclusion

The case presented here supplements the scarce available data on the utility of GLP-1 receptor agonist therapy in combination with an intensive insulin regimen. The use of these agents with rapid-acting insulin is uncommon, possibly because they both target postprandial blood glucose or because the combination does not have FDA approval. However, limited published studies demonstrate that this can be an effective strategy for patients requiring very high doses of insulin. Indeed, many practitioners are using this combination off-label and anticipate that the FDA will approve this use in the future. The use of GLP-1 receptor agonists in patients on basal insulin alone is safe and has been approved by the FDA.

The potential benefits of adding GLP-1 receptor agonist therapy to insulin include weight loss, improved glycemic control, and enhanced safety compared to combination sulfonylurea and insulin therapy. The potential disadvantages are gastrointestinal side effects and the risk of hypoglycemia if the doses of concurrent hypoglycemic medications are not titrated down as patients' glucose levels improve on GLP-1 receptor agonist therapy. Also, the concerning documented reports of pancreatitis and thyroid C-cell tumor formation should be kept in mind.

For motivated patients who maintain good communication with their clinician, this regimen can vastly improve quality of life and assist in attaining previously unattainable glycemic goals. All parties must respect that this combination falls outside

of published guidelines and is not FDA-approved and, therefore, must be used with caution. Until there is more evidence in support of this strategy, the combination of a GLP-1 receptor agonist and prandial insulin should be undertaken only under the supervision of a diabetes specialist.

Duality of Interest

No potential conflicts of interest relevant to this article were reported.

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