



CASE STUDY

A 59-Year-Old Man With Type 2 Diabetes Mellitus Not Controlled on Dual Therapy

Presentation

The patient is a 59-year-old Hispanic man. He has been treated for hypertension and elevated cholesterol levels for several years. One year ago at a follow-up visit, his fasting plasma glucose (FPG) level was 160 mg/dL, his body mass index (BMI) had reached 30.7 kg/m², and he was diagnosed with frank type 2 diabetes mellitus (T2DM). His clinician initiated therapy with metformin 1000 mg twice a day, provided strict dietary guidelines, and strongly suggested that he begin regular weekly exercise. The patient reluctantly agreed to the treatment regimen. He had also been resistant to begin treatment for his hypertension and hypercholesterolemia because he experienced no symptoms and felt quite healthy. While he agrees to take the metformin, he remains skeptical about the T2DM diagnosis. He admits that he has gained weight but does not believe he is obese. His work requires hard physical labor all day, but he enjoys his wife's fine cooking and sees no need for diet restriction and more exercise.

At a follow-up visit 3 months ago, the patient's glycosylated hemoglobin (A1C) value exceeded 8%. The physician added the sulfonylurea glipizide in an effort to control his hyperglycemia.

At his current appointment the patient is very agitated. He reports that he felt fine a year ago, before he started "all these crazy medications," and now he feels awful. He has been having frequent episodes of draining fatigue as well as periods of lightheadedness; in his words, he "came close to passing out and had to hold on to a table to keep from falling." Now and then his heart races so terribly he can hear it pounding in his chest. He says he has always been a calm person but is now nervous and jumpy. He wants to know, is this because his illness is getting worse, or is it that his treatment is not working?

Current Medications

- Losartan 50 mg daily
- Atorvastatin 10 mg daily
- Metformin 1000 mg twice a day
- Glipizide 10 mg twice a day

Physical Examination

- BP 132/82 mm Hg
- Weight 198 lb
- Height 5 ft 8 in
- BMI 30.1 kg/m²
- Heart rate 94 beats per minute

BP = blood pressure.

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Laboratory Results

- A1C 8.2%
- Serum creatinine 0.8 mg
- Lipid panel:
 - TC 188 mg/dL
 - LDL-C 115 mg/dL
 - HDL-C 41 mg/dL
 - non-HDL-C 147 mg/dL
 - TGs 160 mg/dL

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; TGs = triglycerides.

The American Diabetes Association (ADA) recommended goals for adults with diabetes include BP <130/80 mm Hg and LDL-C <100 mg/dL.¹ The patient is not quite at these levels but has responded to the angiotensin receptor blocker (ARB) and statin. If he is able to adhere to the recommended lifestyle modifications, his response should improve. Of additional concern is his A1C level of 8.2%, which correlates with a mean plasma glucose level >200 mg/dL.¹ It is also clear that the patient remains in denial about his obesity. His likelihood of nonadherence is now further aggravated by the physical symptoms he describes, which he is convinced are a result of his treatment regimen.

Clinical Decision Point

What changes in therapy should be made at this point?

- Switch to another antihypertensive agent
- Add a third oral antidiabetic agent, such as a glitazone
- Discontinue the sulfonylurea
- Intensify patient education and counseling

Comment

As long as this patient believes that treatment is making him feel worse rather than better, he is unlikely to agree to undertake a program of diet and exercise, particularly if he is feeling fatigued and lightheaded. It is not likely that these symptoms are caused by the ARB he is taking for hypertension. The addition of a third oral agent to achieve A1C control is somewhat reluctantly recommended by the ADA and the European Association for the Study of Diabetes (EASD) due to concerns about efficacy and cost-efficiency.² An algorithm for the management of T2DM is shown in Figure 1.² An additional effective strategy that has not been fully employed in this patient is to refer him for comprehensive diabetes self-management education, which includes ongoing consultation with a certified diabetes educator (CDE). A meta-analysis has shown that this can lower the A1C by as much as 0.76%.³

The most likely cause of the patient's symptoms is episodes of hypoglycemia, a common adverse effect of treatment with sulfonylureas. These episodes are seldom severe enough to result in comas or seizures, but they can be disruptive and distressing to patients.² Thus, the initial change in this patient's therapy is to discontinue the glipizide while maintaining his regimen of metformin, the ARB, and the statin. At the same time great benefit is to come from intensive, ongoing diabetes education and lifestyle counseling.

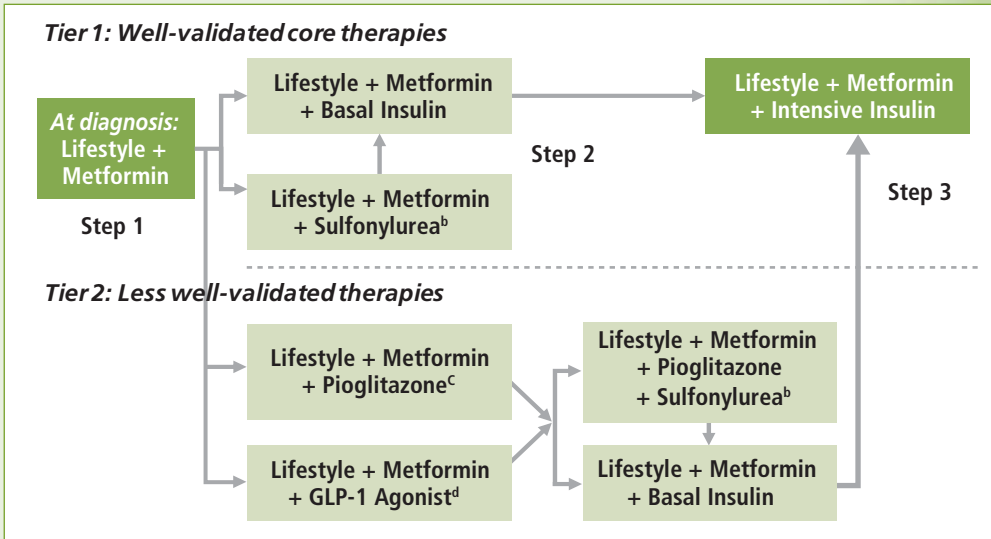


Figure 1. ADA/EASD: Consensus algorithm for initiation and adjustment of therapy for T2DM.^a

^aReinforce lifestyle interventions at every visit. Check A1C every 3 months until <7% and then at least every 6 months; ^bOther than glyburide or chlorpropamide; ^cOption if hypoglycemia is particularly undesirable. Associated with increased risks of edema, congestive heart failure, and fracture; ^dOption if hypoglycemia is particularly undesirable or weight loss is a major consideration and A1C is <8%. Associated with relatively high frequency of nausea, vomiting, and diarrhea. Insufficient clinical use for confidence regarding safety. Nathan DM et al.²

Decision: Discontinue glipizide; intensify patient education and counseling.

The patient's regimen now consists of metformin monotherapy 1000 mg twice a day and working with the CDE regularly, maintaining contact by telephone. With the CDE's instruction, he learns about proper diet and how to use the glucometer and agrees to monitor his FPG level at least 3 times per week. He understands even moderate weight loss yields specific benefits in terms of decreased insulin resistance, better glycemic control, and lowered BP! The focus of his work with the CDE is to increase the patient's understanding of his condition so that he will be aware of the serious risks posed by poor glycemic control and see that there is an effective way to achieve optimal control. The objective is not to frighten him into adherence but to demonstrate that there is a reliable pathway to long-term good health.

At the 3-month follow-up visit, the patient reports no further hypoglycemic symptoms after the withdrawal of glipizide. He has been in regular contact with the CDE, is monitoring his FPG level 3 times weekly, and takes his medications as prescribed.

Physical Examination

- Weight 191 lb
- BP 138/86 mm Hg
- FPG 110-130 mg/dL
- A1C 7.4%

The patient is pleased that his A1C level has diminished by 0.8%, but he is discouraged that he has been unable to lose more weight despite his efforts. Discussions with the CDE

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have made him aware that his excess weight presents a definite threat to his long-term health and well-being. His healthcare providers present him with alternative treatment options for bringing his A1C level to goal. One of these is the addition of basal insulin, which is recommended by the ADA as the most effective and cost-efficient means of lowering A1C. He is also told that insulin can often cause weight gain. In fact, the ADA specifically recommends insulin for T2DM patients whose hyperglycemia has progressed to the point of significant weight loss despite unchanged dietary intake.¹ The patient emphatically rejects insulin therapy, and the healthcare team considers other therapeutic options.

Clinical Decision Point

What therapeutic options should be considered at this point?

- Add a thiazolidinedione, such as rosiglitazone or pioglitazone
- Reintroduce a different sulfonylurea, such as glimepiride or glyburide
- Add an incretin mimetic
- Add an α -glucosidase inhibitor

Comment

Concern about the increased risk of weight gain and possible heart failure with thiazolidinediones makes this class of drugs unattractive for this patient. Given this patient's adverse reaction to 1 sulfonylurea, switching to an agent of a different class may be preferable. Data on both dipeptidyl peptidase-IV (DPP-IV) inhibitors and α -glucosidase inhibitors suggest that they may provide a degree of glucose-lowering, but are unlikely to contribute to weight loss. However, the specific mechanism of action of the incretin mimetic may offer an effective pathway to lowering this patient's A1C level while also supporting his weight loss goals.

Decision: Add an incretin mimetic.

At the present follow-up appointment, the patient's FPG range is within the range recommended by the ADA (90-130 mg/dL). His A1C level, however, is well above the recommendations, which are shown in Table 1.⁴

A1C, PPG, and FPG

There is evidence that the relative contributions of FPG and postprandial plasma glucose (PPG) to A1C shift markedly as A1C values decrease. At the lower end of the scale, PPG contributes much more to A1C than does FPG.⁵ Figure 2 (page 97) shows the relative contributions of PPG and FPG to A1C in each of 5 A1C quintiles.⁵

This patient's A1C (7.4%) is closer to the lower end of this scale, so it is likely that addressing his postprandial insulin needs would be an effective means of enhancing glycemic control.

Table 1. Targets for Glycemic Control

	ADA	AACE/ ACE
A1C (%) Normal: 4%-6%	<7.0	≤6.5
Fasting/preprandial (mg/dL)	90-130	<110
Postprandial (mg/dL) (2 h)	<80	<40

AACE = American Association of Clinical Endocrinologists; ACE = American College of Endocrinology. American Diabetes Association¹; AACE Diabetes Mellitus Clinical Practice Guidelines Task Force.⁴

What Information About Type 2 Diabetes Mellitus Will Most Improve Patient Adherence?

It is not an overstatement to describe diabetes as an epidemic. It is estimated that >7.8% of Americans have diabetes—approximately 23 million people. About one quarter of these have not been diagnosed and are unaware that they have this disease.¹ This is of considerable concern, since the implication is that many or most persons with diabetes are not diagnosed until some complications appear.²

The progression of diabetes represents a failure of homeostasis. When the body's needs for insulin to metabolize glucose for energy are precisely met by the capacity to secrete insulin, a state of balance exists. In the nondiabetic individual, increasing levels of plasma glucose stimulate insulin secretion in pancreatic β cells. The fundamental defects in T2DM are glucose insulin resistance and progressive β -cell failure. There is progressive dysfunction of the insulin-secreting β cells, resulting in insufficient insulin to metabolize the glucose present in plasma. At the time of diagnosis as much as 80% of β -cell function may have been lost and perhaps 50% of β -cell mass may have been lost.³ Resistance to insulin by insulin receptors causes whatever amount of insulin is being secreted by β cells to be progressively less effective. It is thought that there are genetic as well as environmental factors contributing to both of these defects. The principal environmental factors are excessive body weight and physical inactivity; exercise, normal body weight, and prudent diet have been demonstrated to increase insulin sensitivity.⁴

A simplified way to describe this to a patient is to say that the body tries to cope with the task of turning increasing amounts of blood sugar into energy by stepping up insulin production until the cells that secrete insulin can no longer meet the demand, while at the same time the insulin receptors lose their sensitivity to insulin and do not respond as well. In other words, blood sugar overwhelms the body's capacity to deal with it. The progression of T2DM, from normal glucose tolerance, to impaired glucose tolerance, to frank diabetes is shown in the Figure.⁴ Diagnosis of T2DM typically takes place a decade after insulin resistance has begun; however, events leading to the microvascular and macrovascular complications begin at the start of this progression and damage often is present at the time of diagnosis.⁴

Early intervention with lifestyle modification can slow progression to frank T2DM. The Diabetes Prevention Program, which enrolled more than 3000 nondiabetic persons with

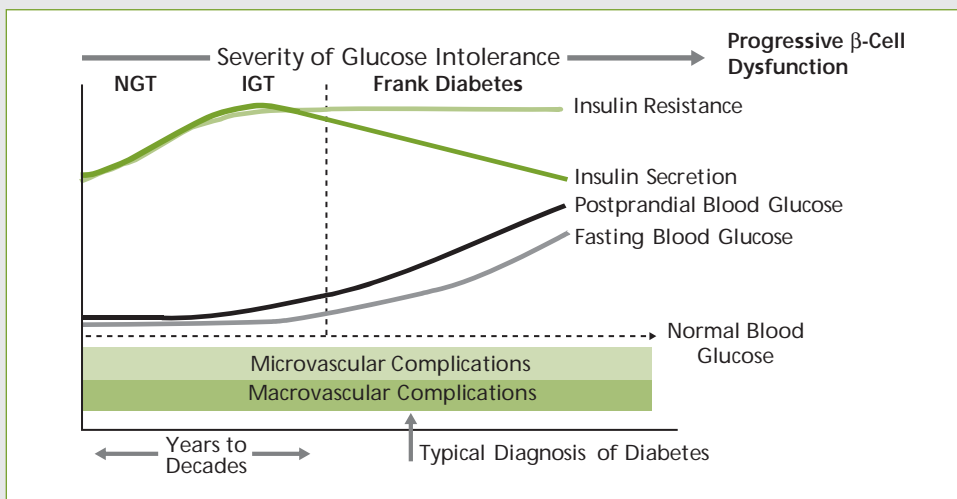


Figure. Natural history of type 2 diabetes. IGT = impaired glucose tolerance; NGT = normal glucose tolerance. Leahy JL.⁴

What Information About Type 2 Diabetes Mellitus Will Most Improve Patient Adherence? (continued)

elevated FPG and PPG levels, compared lifestyle modifications with metformin and placebo; lifestyle measures resulted in significantly greater weight loss than metformin (5.6 vs 2.1 kg, $P < .001$) and significantly less progression to T2DM (58% vs 31% lower than placebo, $P < .001$).⁵ Participants in the intensive lifestyle intervention group followed a low-calorie, low-fat diet, and exercised at moderate intensity, such as brisk walking, for at least 150 minutes per week. The goal for participants in this group was to achieve and maintain weight reduction of at least 7%. Group members attended a 16-lesson curriculum taught one-on-one by case managers during the first 24 weeks postenrollment. Education covered diet, exercise, and behavior modification and was individualized according to participant needs. Group and individual sessions with case managers were scheduled monthly after the initial 24-week intervention to help reinforce behavioral changes.⁵ Fifty percent of the group reached the target 7% weight loss by the end of the 24-week curriculum, and 38% had weight loss of at least 7% at the time of the most recent visit.⁵

It is important to ensure that patients understand how crucial self-management is in the treatment of T2DM. Although patients see their healthcare providers at regular intervals, they must closely monitor their own glycemic control and weight. Self-monitoring of blood glucose and moderate weight loss yields specific benefits in terms of decreased insulin resistance, better glycemic control, and lowered BP.² Healthcare professionals need to acknowledge for their patients that sustained weight loss is difficult and requires persistence, and patients should not be discouraged at initial failures to lose significant weight or fluctuations in weight; in the long term, weight loss efforts will pay off.

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Faulty First-Phase Insulin Response

The rationale for moving to an incretin mimetic is based on an understanding of the first-phase insulin response and the role of the incretin system. Insulin is secreted by β cells in response to stimulation by glucose as well as other insulin secretagogues like sulfonylureas. Secretion takes place in 2 distinct phases: one, a rapid first-phase response commencing immediately after glucose ingestion; the other, a slower, continuous response, which is detectable only after the first-phase response has abated. Patients with diabetes exhibit marked postprandial hyperglycemia. In a study that compared 16 patients with uncontrolled T2DM with 14 patients without diabetes, it was found that even though their fasting insulin levels were similar, the patients with diabetes secreted much less insulin immediately after meals and, as a result, had much higher increases in PPG levels.⁶

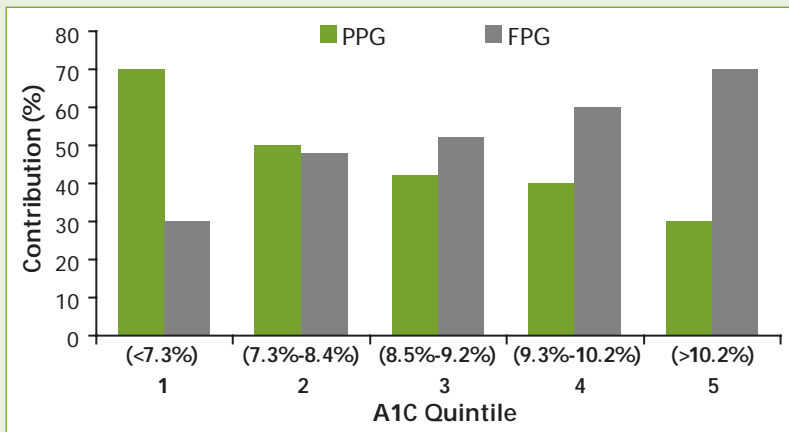


Figure 2. At lower A1C levels, PPG contributes more to overall A1C than FPG. Monnier L et al.⁵

Incretins and First-Phase Response

Several studies have demonstrated the interesting fact that plasma levels of insulin are higher after oral ingestion of glucose than after intravenous administration, focusing attention on peptides released in the gut in response to foods that potentiate the secretion of insulin. Several of these peptides, termed incretins, have been evaluated for their potential in the treatment of T2DM, in particular their contribution to the postprandial or early insulin response. Two in particular are glucagon-like peptide (GLP-1) and gastric inhibitory peptide (GIP). These incretins have a unique mode of action, potentiating insulin secretion only when serum glucose is above a certain base level, whereas other insulin secretagogues stimulate insulin secretion regardless of physiologic need.^{7,8} Other incretin-triggered pancreatic effects include increased proinsulin biosynthesis, increased β -cell survival, decreased apoptosis, and decreased glucagon secretion.⁹ Moreover, incretins appear to trigger a variety of beneficial extrapancreatic effects (Table 2).¹⁰

Thus, manipulation of the incretin system may be a good way to address this patient's likely deficiency in rapid insulin response. There are 2 strategies available to mobilize the therapeutic potential of the incretin system (Table 3).¹¹ Because native GLP-1 is degraded very rapidly by the DPP-IV enzyme system, 1 strategy is to use an

Table 2. Incretin System Extrapancreatic Effects

Organ	Incretin Effect(s)
Liver	Decreased hepatic gluconeogenesis
Brain (hypothalamus)	Decreased appetite, increased satiety, decreased food/water intake
Stomach	Decreased gastric emptying, decreased acid secretion

Drucker DJ et al.¹⁰

Table 3. Therapeutic Potential of the Incretin System

- Incretin mimetics
 - Mimic many of the glucoregulatory effects of GLP-1
 - May preserve β -cell function
 - Resistant to DPP-IV
- GLP-1
 - Rapidly degraded (<2 min) by DPP-IV
- DPP-IV inhibition
 - Extends endogenous GLP-1 half-life

Drucker DJ.¹¹

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agent that inhibits this enzyme. Several DPP-IV inhibitors have been shown to potently inhibit DPP-IV activity after oral administration, causing a 3- to 5-fold increase in native GLP-1 levels.¹⁰ The 2 most studied are vildagliptin and sitagliptin, although only sitagliptin is currently approved for use. The addition of vildagliptin to metformin in patients with T2DM resulted in a lowering of A1C of 0.8% at 12 weeks, compared with placebo. A phase 3 clinical trial with sitagliptin found that it was well tolerated either as monotherapy or with other orally administered DPP-IV inhibitors and did not result in either hypoglycemia or weight gain.¹⁰ Clinical experience with DPP-IV inhibitors, however, is somewhat limited, and there are indications that the DPP-IV enzyme system is widely distributed through human tissues, including T cells responsible for cellular immunity. Thus, it remains to be seen whether inhibition of this enzyme will adversely perturb immune-related activity in human subjects.¹¹

Potent Incretin Mimetic

Another avenue is to employ an incretin mimetic. Exenatide is a naturally occurring GLP-1 receptor agonist isolated from the venom of the *Heloderma suspectum* lizard, known as the Gila monster. It mimics all the glucose-lowering actions of GLP-1 and is several orders of magnitude more potent than native GLP-1 following parenteral administration.⁷ Numerous clinical trials have evaluated the efficacy of exenatide in patients with T2DM. Table 4 compares the actions of GLP-1, exenatide, and DPP-IV inhibitors.¹⁰ While exenatide and the DPP-IV inhibitors both lower A1C, they differ in their effects on weight loss.¹⁰

Incretin Effect: Weight Loss

The capacity of exenatide treatment to result in weight loss is of particular interest with regard to this patient. In an 82-week trial consisting of 30 weeks of placebo-controlled study followed by a 52-week extension, subjects taking exenatide plus either metformin or

Table 4. Incretin Mimetics Can Accentuate Many Properties of GLP-1

	GLP-1	Exenatide	DPP-IV Inhibitor
↑ Glucose-dependent insulin secretion	✓	✓	✓
↓ Glucagon secretion	✓	✓	✓
↓ Hepatic glucose output	✓	✓	✓
Regulates gastric emptying	✓	✓	Marginal
↓ Rate of nutrient absorption	✓	✓	No obvious effect
↓ Food intake	✓	✓	No obvious effect
↓ Plasma glucose acutely to near-normal levels	✓	✓	✓
Resistant to DPP-IV degradation		✓	
Duration in plasma following a subcutaneous (SC) injection	Short	Long	Long

Drucker DJ et al.¹⁰

a sulfonylurea lost an average of 4.4 kg from their baseline weight. Weight loss was greater in patients with higher baseline BMI values, ranging from 2.9% of body weight for those with BMIs <25 to 5.5% for those with BMIs \geq 40.¹²

Exenatide's potential to induce weight loss was demonstrated in a crossover trial comparing exenatide 10 μ g twice a day with daily insulin glargine, an analog basal insulin. The trial enrolled 138 patients with T2DM who had not attained glucose control despite treatment with metformin or sulfonylurea. From the start to the crossover point at 16 weeks, the exenatide group lost on average 2.0 kg, while the insulin glargine group gained 1.0 kg. As soon as they were crossed over, the tracks changed direction. Patients who had been on insulin who were switched to exenatide lost 2.2kg, while those who had been on exenatide and switched to insulin gained 2.3 kg.¹³ There seems to be no connection between nausea and the weight loss effect of exenatide, which persists after nausea diminishes.¹⁴

In the 2 studies described previously, patients treated with exenatide achieved A1C decreases exceeding 1%. In the 82-week trial, the reduction in A1C at week 82 was 1.1%,¹³ while in the crossover trial, the exenatide and glargine groups demonstrated similar reductions in A1C (-1.36% from baseline values of approximately 9.0%).¹³

Trough and Peak Plasma Glucose

While insulin is capable of bringing about larger decreases in plasma glucose than other treatment modalities including incretin mimetics, exenatide's mechanism of action clinically results in significant differences in the blood glucose profiles that may be of benefit to many patients. Exenatide and insulin glargine were compared in an open-label study of 551 patients with T2DM who were inadequately controlled on metformin and sulfonylurea and found to lower A1C by a similar amount, approximately 1%, from mean baseline values of 8.2% to 7.1% after 26 weeks of treatment (Figure 3).¹⁵ Patients receiving insulin attained lower FPG levels than those taking exenatide, and a larger proportion of insulin-treated patients achieved FPG levels below 100 mg/dL than those on exenatide (21.6% vs 8.6%). However, patients taking exenatide had significantly lower glucose levels

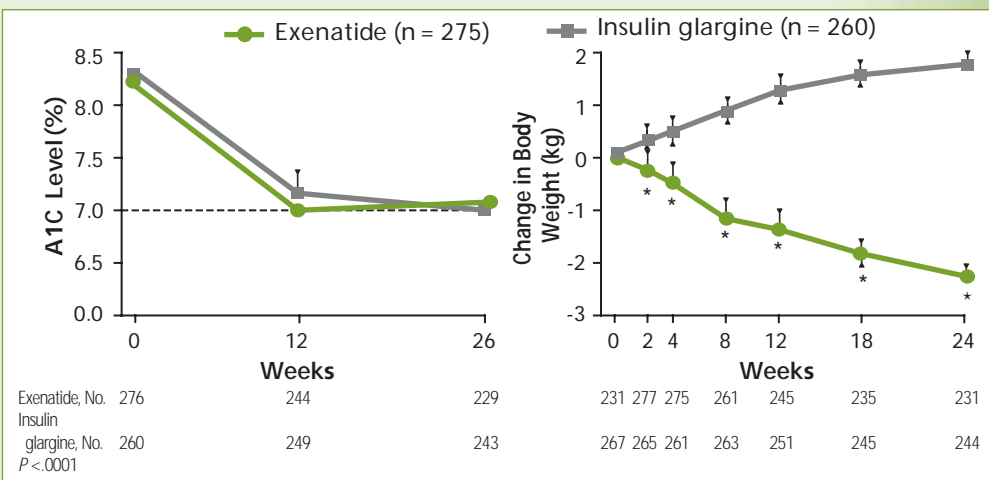


Figure 3. Exenatide vs insulin glargine in type 2 diabetes: effects on A1C and body weight. Heine RJ et al.¹⁵

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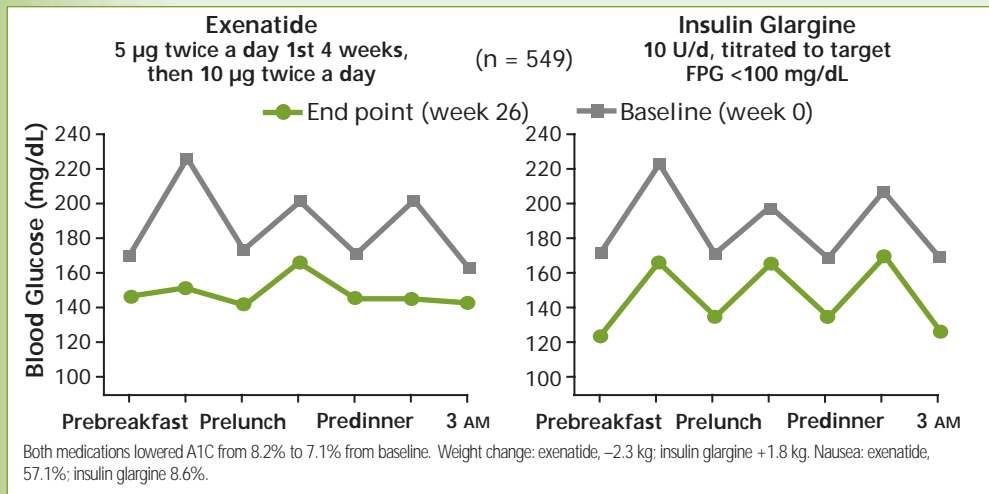


Figure 4. Open-label, twice-daily exenatide vs once-daily insulin glargine: self-monitoring blood glucose profiles. Heine RJ et al.¹⁵

($P < .0001$) after meals than those receiving insulin; exenatide reduced PPG excursions more than basal insulin. The overall rate of hypoglycemia was similar across treatment groups at 7.3 events/patient-year in the exenatide group versus 6.3 events/patient-year in the insulin glargine group. Figure 4 compares plasma glucose levels during the 24-hour period with exenatide and insulin glargine.¹⁵ As in other studies, exenatide treatment was associated with weight loss and insulin with weight gain.¹⁵

Because of the patient's ongoing weight issues, the clinician decides to prescribe exenatide 5 µg twice a day, the dose used for initiation of therapy. Although the patient is nervous about the injections, he agrees to a trial. The patient tolerates the drug well and at the end of the 1-month initiation period, the exenatide is increased to a 10-µg twice a day maintenance dose. Unlike insulin, exenatide is not titrated in relation to blood sugar levels.

After about 10 weeks on this new treatment regimen, the patient requests an appointment. He has been monitoring his plasma glucose and he thinks it is headed in the right direction. He also reports that he has been losing weight. However, since being on exenatide 10 µg twice a day, he has been having frequent episodes of mild nausea.

Clinical Decision Point

How should this patient's treatment be continued at this time?

- Add a daily antiemetic
- Decrease the exenatide dose to 5 µg
- Keep the dose constant but try smaller portions at meals
- Replace exenatide with another oral antidiabetic drug

Comment

This patient's treatment plan is having results and does not call for drastic changes such as switching to an orally administered DPP-IV inhibitor or attempting to suppress the nausea with an antiemetic. Nausea is the most common adverse effect associated with exenatide. Nearly 50% of patients receiving exenatide 10 µg experience nausea during the first 8 weeks of treatment; the incidence is lower in patients on the 5-µg dose and declines as treatment continues.¹⁷

The risk of hypoglycemia with exenatide in combined therapy with metformin is no higher than with placebo. The risk is higher when exenatide 10 µg is given with a sulfonylurea, in which case consideration should be given to lowering the dose of the sulfonylurea or eliminating it all together. Other adverse events noted in US Food and Drug Administration postmarketing reports include several reports of acute pancreatitis and rare cases (6) of hemorrhagic and necrotizing pancreatitis, of which 2 have been fatal. A causal relationship between exenatide and pancreatitis has not been established. Exenatide should be immediately discontinued if pancreatitis is expected.¹⁷

Decision: Decrease the exenatide dose to 5 µg twice a day.

After a month on the exenatide 5-µg twice a day dose, the patient's nausea has subsided and he returns to the 10-µg twice a day dose with no further nausea. He returns for his regular 3-month follow-up visit and is encouraged that his weight loss has brought him below the marker for obesity, although he is still overweight.

Physical Examination

- Weight 181 lb
- BMI 27.5 kg/m²
- BP 131/80 mm Hg
- FPG 90-110 mg/dL
- A1C 6.6%

The patient's A1C value is evidence of good glycemic control. Further weight loss is desirable, and he will work toward that goal with his healthcare providers and the CDE. The episodes of hypoglycemia that he had been experiencing when he was first diagnosed with T2DM have not returned, nor has the nausea he was feeling when he was initially on exenatide.

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