

Case Study: A 62-Year-Old Man With “Brittle” Type 1 Diabetes

Jeff Unger, MD

Presentation

K.A. is a 62-year-old man with a 42-year history of “brittle” type 1 diabetes. When first seen at our office, he complained of erratic and unpredictable blood glucose levels despite adhering to a rigid multiple daily insulin injection protocol. He was taking four insulin injections per day (NPH before breakfast and at bedtime and lispro insulin (Humalog) before each meal) and performing self-monitoring of blood glucose (SMBG) eight times daily, including pre- and postprandially and whenever he felt symptomatic. K.A. injected his morning NPH in the abdomen, his lunch and dinner insulin in the arms, and his bedtime NPH in the buttocks.

He was sedentary and did not exercise. He had been counting carbohydrates to adjust his insulin for only 5 months.

Five years ago, K.A. developed frequent severe hypoglycemia, during which he lost consciousness and presented in the hospital emergency room. His blood glucose levels had been <30 mg/dl on each of his eight emergency room visits. In the ensuing 5 years, he had developed hypoglycemic unawareness.

Because of the frequency of hypoglycemic events with altered levels of consciousness (at least 30 episodes documented per month) the patient’s driver’s license was revoked, and he sought an early retirement from his job as an electrical engineer. He believed that his control might improve if he were placed on an insulin pump.

K.A. is 71 inches tall and weighs 74 kg. His blood pressure at our initial visit

was 124/86 mmHg without orthostatic changes. His diabetes-related complications included autoimmune hypothyroidism, microalbuminuria, peripheral sensory neuropathy, and nocturnal diarrhea. His HbA_{1c} was 7.3%, and his fasting capillary blood glucose was 125 mg/dl. His liver function was normal, but he did have proteinuria (245 mg/dl in a 24-h urine collection). His creatinine was 1.2 mg/dl. His thyroid and adrenal function studies were normal.

After unsuccessful attempts to fine-tune his insulin injections based on carbohydrate counting and preprandial glucose readings, we placed him on continuous subcutaneous insulin infusion (CSII) therapy. Unfortunately, K.A. did not experience any improvement in his glycemic control. He became more depressed and frustrated because he was still experiencing daily hypoglycemic events. After 2 weeks of insulin pump therapy, he was placed on a continuous glucose monitoring system (CGMS).

Figure 1 shows the results of his CGMS test. Analysis of the sensor readings demonstrated that the patient’s SMBG records were not consistent with those obtained by interstitial fluid sensing. At 8:00 a.m., the patient’s meter (circle markers in Figure 1) read 298 mg/dl, but the sensor reading (dark line in Figure 1) was 118 mg/dl. When he believed that his blood glucose was high based on erroneous meter readings, he would give himself a compensatory bolus of insulin via his pump. There was no consistent correlation between the sensor and the meter. Thus, K.A. was constantly administering insulin based

on inaccurate SMBG readings. The disparity between the sensor and the meter was so substantial that the sensor would stop functioning and have to be recalibrated by the patient throughout the day. (See Figure 2.) This indicated a problem with the meter, rather than a malfunctioning of the CGMS.

When the patient was informed about the inaccuracy of his meter, he explained that he had purchased the device, which used test strips, 10 years ago and he had never doubted its accuracy. Although reluctant to part from his favorite meter, the patient’s diabetes control improved when he was provided with a more accurate device. Two months after receiving his new meter,

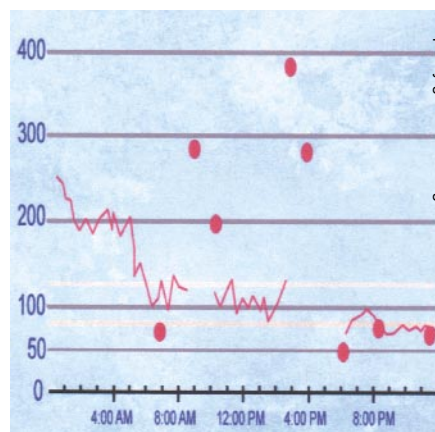


Figure 1. A CGMS test shows a disparity between the results of the patient’s SMBG (circles) and the interstitial glucose readings obtained by the sensor (dark line). The differences between the two types of readings were so substantial that the sensor had to be recalibrated on two occasions as shown by the breaks in the sensor graph.

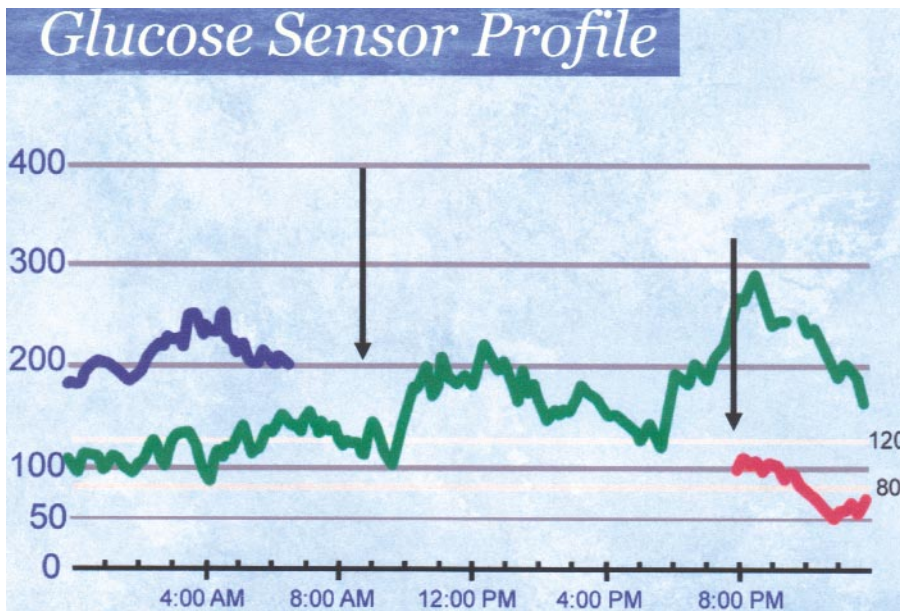


Figure 2. Gaps in the sensor tracing indicate the disparity between the patient's interstitial glucose readings and the blood glucose levels obtained with the home glucose meter.

K.A. reported that he was no longer experiencing any hypoglycemic episodes and was feeling so well on his insulin pump that he began to work part-time and hoped to have his driving privileges re-instated. The CGMS test was repeated and showed no hypoglycemic events and improved overall glycemic control.

Questions

1. What is the differential diagnosis of recurrent severe hypoglycemia in type 1 diabetes?
2. How should providers approach type 1 diabetic patients with severe hypoglycemia?

Commentary

Multiple causes of widely erratic glycemic control are seen in patients with longstanding type 1 diabetes. A careful history should be performed to explore causes related to diet, monitoring, medications, and activity. Testing should be directed at detecting occult liver and renal disease and thyroid and adrenal insufficiency. Patients may have delayed gastric emptying, which can result in postprandial hyperglycemia or hypoglycemia. Lipohypertrophy may

affect insulin absorption, and differences in absorption and onset of action of intermediate- and long-acting insulins may cause wide glycemic variations. Occasionally, the preprandial dose of short-acting insulin does not match the anticipated rise in blood glucose levels that occurs with a given carbohydrate intake. Exercising during insulin peak times may also cause hypoglycemia. Patients who have had type 1 diabetes for more than 5 years develop decreased hypoglycemic counterregulation due to a diminished glucagon secretory response and diminished epinephrine secretion in response to hypoglycemia.

A novel way to determine the etiology of "brittle diabetes" is to place the patient on a CGMS. The CGMS is slightly larger than an insulin pump and is inserted painlessly into the subcutaneous tissue of the abdomen. After calibration, interstitial glucose levels are analyzed and stored every 5 min. Thus, ~300 glucose readings are evaluated during a 24-h period.

A well-calibrated blood glucose meter should always be used while on the sensor. The patient wears the CGMS device for 3 days. The data are then

downloaded into a personal computer, and a printout depicting nearly 900 glucose readings over a 3-day period is generated for analysis.

The CGMS allows a physician to evaluate trend analysis of the multiple interstitial glucose readings rather than relying on four or five daily fingerstick glucose levels. Using the CGMS, physicians can easily evaluate the effects of different foods on glycemic control, determine the presence of nocturnal or diurnal hypoglycemia, analyze postprandial glucose excursions, evaluate the effect of oral agents and different insulins on glycemic control, document the effect of different exercise programs on glycemia, and even determine the accuracy of the patient's SMBG meter.

Patients are often stunned to learn that they have hypoglycemic unawareness or significant postprandial hyperglycemia in response to eating their favorite type of pizza. The documentation derived from CGMS analysis may allow physicians to improve overall control and prevent nocturnal hypoglycemia.

Using the CGMS, K.A. was able to regain the glycemic control that he had not had for at least 10 years. His insulin pump is now allowing him to return to work and enjoy life without having to frequent the emergency room for treatment of severe hypoglycemia.

Clinical Pearls

- Physicians should always evaluate the reason for their patients' "brittle diabetes." Table 1 lists common causes of wide glycemic variations.
- Before initiating an extensive workup in individuals with widely fluctuating blood glucose levels, physicians should evaluate the accuracy of the patient's home glucose meter. Patients should be instructed on how to clean, calibrate, and properly use their meters. If the meter is determined to be accurate, CGMS may be helpful in determining how a patient's pharmacological therapy should be altered to improve glycemic control to reduce hypoglycemia and hyperglycemia.

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Table 1. Common Causes of “Brittle Diabetes”

- Undiagnosed thyroid, adrenal, kidney, and/or liver disease
- Inconsistent insulin injection site rotation
- The use of large doses of insulin, which can slow absorption and alter peak onset and duration of action
- Patient confusion on insulin dose determination
- Concomitant use of oral medications (corticosteroids, insulin sensitizers), which can affect patients’ blood glucose levels
- Underlying infection, which may cause insulin resistance
- Use of home glucose meters that are improperly maintained and calibrated

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Note of disclosure: Dr. Unger has received honoraria for speaking engagements from Medtronic MiniMed, which manufactures continuous subcutaneous insulin infusion systems and the continuous glucose monitoring system.

Case Study: Chronic Vomiting in a Patient With Type 2 Diabetes

Ray E. Clouse, MD, and Patrick J. Lustman, PhD

Presentation

A.M. is a 54-year-old woman who was diagnosed as having type 2 diabetes 8 years ago. She has mild hypertension but no evidence of coronary artery disease or other complications of diabetes. She is managed with insulin and has poor control of hyperglycemia; recent HbA_{1c} concentrations range from 10 to 12%.

One year ago, the patient began having episodic nausea and vomiting. The problem increased in frequency, and for the past 6 months some degree of nausea and vomiting has been present daily. Symptoms occur most commonly in the morning and with eating, when early satiety, bloating, and fullness also are present. Metabolic regulation has wors-

ened, although her weight has remained stable.

Physical examination was normal with the exception of mild obesity. Investigation with endoscopy, hepatobiliary ultrasound, abdominal CT scan, and routine laboratory was unrevealing. A solid-phase gastric emptying study showed mild delay with abnormal radionuclide retention at 2 h. Metoclopramide was transiently effective, and erythromycin produced no benefits.

Questions

1. Does A.M. have gastroparesis?
2. Would a more detailed neuropsychiatric evaluation be helpful?
3. What additional management options could be tried?

Commentary

Chronic nausea and vomiting are particularly detrimental for diabetic patients. The symptoms not only are stressful and uncomfortable, but also interfere with daily functioning and promote deterioration of metabolic control. Vomiting is a source of high hospitalization costs and health care utilization by diabetic patients.

Does A.M. have gastroparesis?

Gastroparesis is defined by the presence of delayed gastric emptying without mechanical obstruction. The abnormality can be demonstrated by retained food on imaging studies or endoscopy following an overnight fast or, more precisely, by delayed clearance of radionuclide on

a quantitative gastric emptying study, as occurred in this case. Obstruction in the antropyloric region, duodenum, or proximal small intestine (e.g., from peptic ulcer disease or tumor) must be excluded as the cause of delayed emptying. This usually is accomplished with endoscopy, as was done for A.M., who indeed has gastroparesis.

Unfortunately, upper gastrointestinal symptoms, especially nausea and vomiting, are too frequently attributed to gastroparesis, which then becomes the focus of therapy. Gastroparesis is found in diabetic as well as nondiabetic subjects and has many causes. Delayed gastric emptying, like slow transit in other gut organs, appears to be one of the gastrointestinal sequelae of diabetes, but because of its many other causes, the relationship of gastroparesis to markers of advancing diabetes (including neuropathy) is only modest in symptomatic patients. As many as 40% of nondiabetic patients with functional nausea and vomiting and no definable pathological explanation for symptoms also have delayed gastric emptying. Thus, gastroparesis should be considered a nonspecific finding in diabetes and may be unrelated to the metabolic disorder.

The relationship of symptoms to delayed emptying is even more precarious in most cases. Gastroparesis typically is asymptomatic in diabetic patients. The poor correlation between degree of symptoms and degree of emptying delay is known, but its acknowledgment has been sluggish, even by the gastroenterological community. Results of treatment trials have further supported the dissociation.

Regular metoclopramide (Reglan) therapy can improve persistent nausea and vomiting in diabetic patients, but many clinicians are unaware that its effects on gastric emptying often are insignificant after as little as 2 months of continuous use. Likewise, the beneficial effects of domperidone (Motilium) (another dopamine-antagonist prokinetic agent that is not approved for use in the United States) on vomiting cannot be attributed to improvement in gastric

emptying. Both of these agents have central antiemetic effects that appear to explain their sustained benefits in clinical practice.

No change in gastric emptying accompanies spontaneous symptom remission in most diabetic patients presenting with vomiting. Thus, the finding of gastroparesis should not restrict the evaluation for alternative causes of nausea and vomiting, nor should it necessarily be attributed to diabetes or limit interventions to approaches that accelerate gastric emptying.

Would a more detailed neuropsychiatric evaluation be helpful?

Finding evidence of peripheral or autonomic neuropathy might offer support for a diabetic etiology to the delay, but it would provide little other direct clinical benefit. Other neurological symptoms and findings are usually present in patients with central nervous system (CNS) diseases that produce vomiting (e.g., malignancy, infarction, infection). Psychiatric symptoms of anxiety or depression are common in patients with functional nausea and vomiting but have the same nebulous role in the initiation or perpetuation of these symptoms as they do in other functional gastrointestinal syndromes.

Nevertheless, resolution of active psychiatric illness may be required to reduce symptoms to an acceptable level. In cross-sectional evaluation of diabetic patients with gastrointestinal symptoms (including nausea and vomiting), psychiatric symptoms predict both the presence and severity of somatic symptoms—in contrast to the poor predictive value of gastroparesis. Consequently, at least a cursory psychiatric assessment may have important treatment implications.

What additional management options could be tried?

The focus on delayed gastric emptying has left under-managed many diabetic patients with chronic nausea and vomiting. “Prokinetic” agents typically are offered first and may be beneficial for

some patients. But the benefits are unlikely restricted to prokinetic actions. As mentioned, metoclopramide and domperidone have pronounced central antiemetic effects that are sustained. Cisapride (Propulsid), now with very limited availability in the United States, was promoted for its prokinetic properties and has more durable effects on gastric emptying than other compounds. This 5HT₄ agonist, however, also favorably influences visceral sensory input to the CNS and potentially through this mechanism has been effective in nondiabetic patients with functional symptoms (with or without gastroparesis). Erythromycin is primarily prokinetic in action, but its beneficial effects in diabetes are limited.

When prokinetic treatment trials are exhausted, clinicians often are at a loss for alternative therapies. Based on the available information, particularly the poor association of gastroparesis with symptoms, we prefer to manage diabetic patients in the same fashion that we would nondiabetic patients with chronic functional gastrointestinal complaints. In some patients, anticholinergics/antispasmodics, as contrary as it may seem, can be beneficial. Other conventional antiemetic agents (e.g., prochlorperazine [Compazine], promethazine [Phenergan]) may be useful, but, because of side effects, are less appealing for chronic, daily use.

Antidepressants, particularly the tricyclic antidepressants in low daily dosage, can be particularly helpful. These medications benefit more than 80% of nondiabetic patients with chronic vomiting syndromes who have failed other approaches, the benefits not conspicuously related to psychiatric drug actions. Preliminary data support a similar efficacy with open-label use of tricyclic antidepressants in diabetic subjects. A.M. was treated and maintained on nortriptyline (Pamelor), 50 mg/day at bedtime, with prompt and sustained response.

Contemporary antidepressants, including SSRIs, may work through a

different mechanism and have been less studied for this indication. We reserve them for patients with active anxiety and/or depression symptoms that may be interfering with treatment response.

Psychotherapy and behavioral interventions also may have a role in refractory cases. Implanted electrical gastric stimulators, initially investigated as potential prokinetic devices, are now being explored actively in diabetic and nondiabetic subjects with chronic nausea and vomiting for their beneficial effects on visceral afferent (sensory) modulation rather than gastric emptying.

Clinical Pearls

- Gastroparesis, or nonobstructive delayed gastric emptying, should not be equated unconditionally with upper gastrointestinal symptoms.
- Most available treatments for nausea

and vomiting in diabetic patients do not exert their dominant effects through improving gastric emptying, at least when used chronically.

- The range of treatments for functional nausea and vomiting in nondiabetic patients, including tricyclic antidepressants, also should be considered in patients with diabetes and chronic symptoms.

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