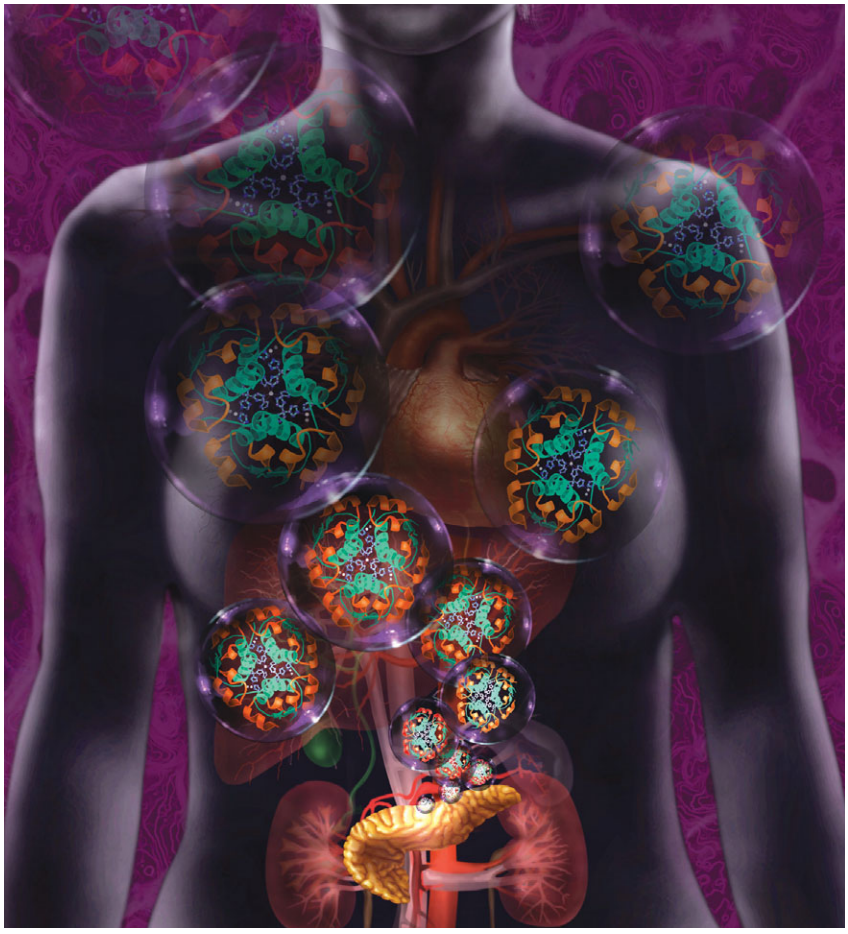
Brittle Diabetes: Drilling Down to the Cause

Four cases illustrate the range of lifestyle problems, treatment complications, and comorbidities that may hold the key to a patient's seemingly intractable glycemic instability.

The term "brittle" has been applied for several decades to patients with severely unstable type 1 diabetes. As defined by Tattersall in 1985, patients with brittle diabetes defy all attempts at improving glycemic control using conventional therapies.[1] Recurrent and long hospital admissions are the rule, so the condition disrupts patients' lives as well as the lives of their families. Most patients with brittle diabetes are in the second or third decade of life and are typically admitted with diabetic ketoacidosis rather than hypoglycemia.

Although finding a specific etiology of "brittleness" can become a challenge for even the most seasoned practitioners, an intuitive approach to the work-up for these patients can lead to clues that might improve erratic glycemic control. Clinicians must be prepared to think outside the box when gathering historical data and performing physical examinations on these patients. Failure to recognize the metabolic and emotional factors that can acutely compromise a patient's glycemic control will result in frequent visits to the emergency department, increased medical costs, higher risk of long-term complications, and possibly, loss of life.

This article describes four patients with type 1 diabetes who have extremely wide glycemic variabilities. The challenge will be to confront and correct the underlying factor or factors in each patient's brittle diabetes, allowing them to live healthier, safer lives.



CASE 1

Ken, a 27-year-old stockbroker, developed type 1 diabetes at age 15. He is

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well known to the emergency department staff and has just presented there for the fourth time in seven months. He complains of nausea, vomiting, hyperglycemia, and "feeling dirty." Ken has been using an insulin pump since 1999.

The emergency team cannot understand why Ken's admissions only occur on Saturday evenings. By Monday morning he will be euglycemic once again and ready for discharge. Ken vehemently denies consuming alcohol, although he admits he "parties" on weekends. A review of his insulin pump and meter downloads demonstrates that he consistently administers insulin and checks his glucose levels even when he becomes ill. His glucose meter downloads show that he has been chronically hyperglycemic for several months. One week ago, an A1c (glycated hemoglobin level) of 8.9% was recorded during a primary care visit.

Ken's blood glucose today is 650 mg/dL, his serum ketones are positive, and his pH is 7.1. This time, a drug screen is ordered, and it comes back positive for marijuana (cannabis). After responding to rehydration and IV insulin infusion therapy, Ken is confronted about his use of illicit drugs. He admits that for the past few years he has been smoking marijuana several times each day, with heavier use on weekends.

Although marijuana can minimize nausea in some people, others can develop a condition known as cannabinoid hyperemesis after years of use.[2] Hyperemesis occurs every few weeks or months, often for many years. Cessation of marijuana use (confirmed by a negative urine drug screen) causes the cyclical vomiting to stop; if use of the drug is resumed, it returns. Patients commonly develop compulsive bathing behaviors in reaction to the hyperemesis.[2]

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Patients who have difficulty achieving good glycemic control after successfully managing their diabetes in the past need a complete physical examination.

Ken's case is unique and important to identify because his glycemic control is complicated by delayed gastric emptying (gastroparesis) as a consequence of constant marijuana use. Dosing insulin against this background is frustrating and challenging for patients, clinicians, and educators.[3] Bolus injections of insulin need to be timed to track with carbohydrate absorption from the gut. For this reason, insulin is injected 15 to 20 minutes before a meal, since carbohydrate absorption begins to occur 30 to 60 minutes after the meal begins.[4] But Ken's stomach doesn't begin to empty until two hours after a meal. By that time, insulin absorption will have peaked, causing Ken to become hyperglycemic. Gastric emptying is further delayed as an individual is exposed to both acute and chronic hyperglycemia.

Ken's brittle diabetes will resolve only if he stops smoking marijuana. He should also be advised by his primary care physician to program and deliver his preprandial insulin as a "square-wave bolus." This should minimize Ken's gastroparesis and favor improved glycemic control.[5]

CASE 2

Mike, a 42-year-old electrician, has been wearing an insulin pump for the past eight years and has achieved excellent glycemic control. However, over the past six months, his A1c has increased from 6.5% to 9%, and his daily glucose variability has ranged from 45 to 400 mg/dL. He is very concerned that his diabetes has become brittle and is afraid of going blind or having a heart attack if his average daily glucose level remains at 320 mg/dL.

Patients who have difficulty achieving good glycemic control after successfully managing their diabetes in the past need a complete physical examination. Physicians should carefully examine insulin injection sites looking for areas of lipoatrophy (Figure). In this condition, injected exogenous insulin causes an immune-mediated subcutaneous process that alters the absorption of insulin.[6] Although less commonly observed with the newer analogue formulations, lipoatrophy can develop with the use of any type of insulin.[7]

Lipoatrophy can be total, partial, or localized. Total lipoatrophy is a congenital or acquired complete loss of adipose tissue, usually associated with hepatomegaly, hyperglycemia, severe insulin resistance, and hyperlipidemia. Partial lipoatrophy is a symmetrical loss of facial fat tissue with or without similar atrophy of the arms and upper trunk. This syndrome has been associ-

ated with renal disease, glomerulonephritis, diabetes, hirsutism, hyperlipidemia, hypocomplementemia, and immunologic disorders. Localized lipoatrophy results in loss of adipose tissue involving multiple areas of the body.

Seeking an explanation for his deteriorating glycemic control, Mike had recently implemented a real-time continuous glucose sensor, which monitored and recorded interstitial glucose levels 300 times a day for seven days. Even so, the etiology of his rise in A1c was not identified until he removed his shirt and a sizable area of localized lipoatrophy was clearly identified. As soon as Mike moved his insulin pump infusion set to a different location, his glucose levels and his A1c normalized. The area of localized lipoatrophy returned to a normal contour within six months of using alternate infusion sites.

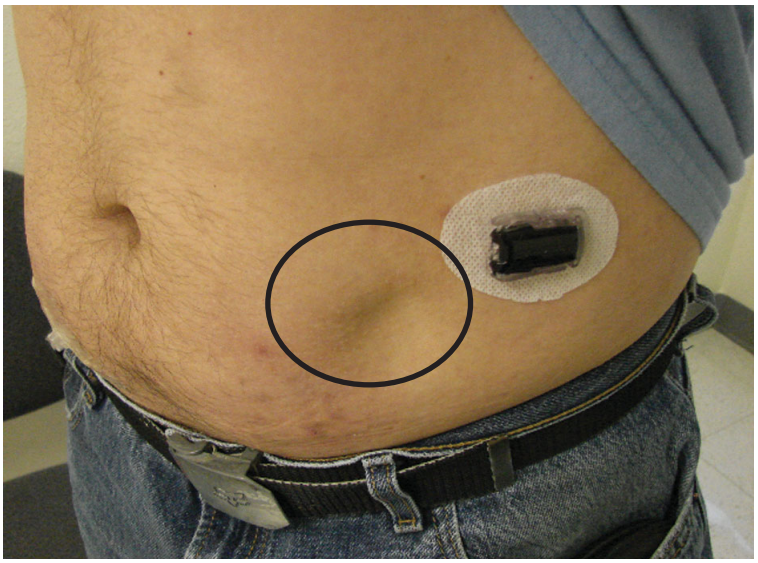

FIGURE. Localized lipoatrophy: The indented area inside the circle was used as the patient's insulin pump infusion site for more than five years. The black device to the right is a real-time continuous glucose sensor. (Photo courtesy of the author.)

CASE 3

Brittany, age 16, has always been a diabetes management nightmare. Diagnosed at age 2 with type 1 diabetes, she has been hospitalized 26 times for diabetic ketoacidosis and 15 times for severe hypoglycemia. Her mom, who is single, jobless, and mentally ill with a history of four suicide attempts, says she is on the verge of giving up hope for Brittany.

Despite wearing an insulin pump, Brittany's A1c levels typically range between 9.5% and 12%. She claims to be "constantly checking my glucose levels," yet she forgets to bring her meter to her primary care physician's office for downloading. The expert care of three pediatric endocrinologists, as well as several certified diabetic educators and registered dietitians, has not improved Brittany's glycemic control. During her last hospitalization, she told the night nurse: "Maybe this world would be a better place without me." Although Brittany has access to excellent clinicians, she continues to be at high risk not only for life-threatening diabetes-related complications but also for suicide.

As a general rule, patients using insulin who are unable to lower their A1c below 9% are simply not following their treatment plans. These patients are omitting injections, neglecting home blood glucose monitoring, skipping their office visits, and failing to refill their prescriptions. Adolescent girls with A1c elevations commonly have an eating disorder and omit insulin in order to lose weight.[8]

Any form of mental illness could severely compromise a patient's ability to successfully participate in diabetes self-management.[9] Think of all the complicated tasks patients with diabetes must perform on a daily basis. They must monitor glucose levels before meals, count carbohydrates, accurately determine preprandial insulin dosages—factoring in their anticipated postprandial activity level and its effect on the pharmacokinetics of the injected insulin—and administer injections 10 to 15 minutes before a meal. Most of them require two or three antihypertensive drugs as well as a statin and an aspirin tablet daily, and they must remember to get their prescriptions filled on time and keep their regularly scheduled office visits with

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TABLE. Common Historical Factors in Patients with Bipolar Depression

- Early onset of initial symptoms (typically before age 25) with episodic presentation
- Family history of mental illness, especially bipolar illness
- Physical, verbal, or sexual abuse during childhood
- Parental divorce, separation, or abandonment during childhood
- Personal or family history of substance abuse
- Previous suicide attempts
- Multiple treatment failures with antidepressants
- Racing thoughts, problems concentrating, anxiety, insomnia, mood swings
- Having enough energy to begin several new projects in spite of sleeplessness, but completing none of them
- History of treatment for attention deficit disorder without responding positively to stimulant therapy
- Previous evaluation by a mental health worker
- Previous incarceration
- Rapid response to an SSRI or SNRI (indicating possible induction of acute mania; most patients do not notice improvement for two to four weeks)

SSRI = selective serotonin reuptake inhibitor; SNRI = selective norepinephrine reuptake inhibitor
Source: Unger J.[16]

their treating physicians. If all these tasks are not daunting enough, try scoring an A1c below 6.5% if you are mentally ill and having visual hallucinations of spiders crawling through your glucose meter! Now you get the picture of the extremely stressful, disrupted, and potentially chaotic lives mentally ill patients with diabetes must continually navigate.

>>FAST TRACK<<

Any attempt to teach intensive diabetes self-management skills will fail if the patient is decompensating emotionally.

Mental illness confers enhanced risk not only of diabetes itself but of hypertension, hyperlipidemia, stroke, and MI, due partly to therapeutic noncompliance and partly to a higher prevalence of harmful habits like smoking, overeating, substance abuse, and sedentary behavior among patients with psychiatric diagnoses.[10-12] Patients with major depression have trouble achieving an A1c below 8%, and their adherence to medication refills is reduced as A1c levels rise above 8%.[13] Except in patients older than age 65, relieving depression has been shown to improve glycemic control.[14]

When dealing with diabetic patients who have psychiatric issues, the physician must always address the mental state before attempting to stabilize the metabolic disease. Any attempt to teach intensive diabetes self-management skills will fail if the patient is decompensating emotionally. Although cognitive therapy may be of some benefit, it has been demonstrated that pharmacotherapy has to be the cornerstone of treatment for the comorbidity of mental illness and diabetes.

Serotonin reuptake inhibitors have been shown to improve depression, A1c levels, and adherence to medication regimens. They also reduce the likelihood of recurrent MI and are associated with lower total medical costs for the long-term care of diabetes.[15] Serotonin norepinephrine reuptake inhibitors are excellent choices for diabetic patients who have depression and multiple painful somatic complaints. Tricyclic antidepressants should be avoided in most diabetic patients due to these drugs' significant side effects, which can exacerbate many of the symptoms associated with diabetic autonomic neuropathy.[8]

On further questioning, Brittany admits to having racing thoughts and severe insomnia. She says she has not slept at all for several days in a row, but still feels highly energized. She reports that she had been placed on an antidepressant six months before, but her symptoms only got worse. The doctor had also put her on two other medications, which she stopped taking because they increased her anxiety. She admits (in strict confidence) that she hopes the hypoglycemia will simply kill her someday. Brittany has bipolar depression, a diagnosis that has been overlooked for years. The Table lists historical factors that should be addressed with patients suspected of having bipolar depression.[16]

Brittany is placed on the mood stabilizer lamotrigine and a combination of the antipsychot-

ics olanzapine and fluoxetine. Her lipids, weight, blood pressure, and waist circumference are checked periodically. Within six weeks, Brittany's moods have stabilized. She is no longer depressed, is sleeping better, is able to concentrate, and is excited about intensifying her diabetes therapy with the help of a certified diabetes educator.

CASE 4

Lisa, a 38-year-old medical office manager, has started having headaches, possibly due to her recurrent hypoglycemia. Stress and anxiety may also be causing the headaches, as well as the canker sores she gets almost every week. Most recently, she received the bad news that she has osteoporosis. Even though she is taking four injections of insulin each day, she can barely control her glucose levels and has constant weight loss and abdominal bloating.

Last month, Lisa's primary care physician diagnosed her with brittle diabetes. He advised her to see a psychiatrist to help her "regain control of her life." She made the appointment but decided to do some medical detective work on the Internet. She found a possible diagnosis and followed the online suggestions. Two weeks later, she was feeling much better. She returned to her primary care physician's office with a self-diagnosis of celiac disease.

Celiac disease causes immune-mediated damage to the jejunal mucosa, which is triggered by gluten, a protein complex found in wheat, rye, and barley.[17] The classic diagnosis is based on demonstrating villous atrophy and crypt hyperplasia in biopsy specimens of the small bowel. Recently, however, health information available online has encouraged patients who think they may have celiac disease to undertake a trial of a gluten-free diet. If their suspicion is correct, reversal of the mucosal abnormalities and symptoms will occur within two to four weeks. Although celiac disease is more common in children, screening studies have shown the prevalence among adults with type 1 diabetes to be between 1.3% and 6.4%, approximately 10 times more common than in the general population.[17]

Many cases of celiac disease are asymptomatic, but some patients have a variety of complaints including fatigue, headaches, canker sores, osteopenia, osteoporosis (secondary to vitamin D and calcium deficiencies), steatorrhea, flatulence, weight loss, depression, anxiety, iron deficiency anemia, and failure to thrive (in children). Autoimmune hypothyroidism is present in 13% of patients with celiac disease, and 4% have Graves disease.[18]

Screening for celiac disease is initiated with serological evaluation using IgA (immunoglobulin A) anti-tissue transglutaminase and IgA endomysial antibodies. Total serum IgA levels should also be obtained, since 5% of the general population does not produce IgA, rendering any IgA-based studies invalid.[19,20] Patients should be maintained on a gluten-containing diet during serological testing.[19,20]

The 2009 American Diabetes Association clinical practice recommendations state that antibody screening should be performed on patients with type 1 diabetes who have possible symptoms of celiac disease, such as iron deficiency anemia, weight loss, or unexplained fatigue.[21] Other tests include measuring tissue transglutaminase or anti-endomysial antibodies, with documentation of normal serum IgA levels.[21] Patients with positive antibodies should be referred to a gastroenterologist for confirmation and to a dietitian for instruction on a gluten-free diet.

Studies suggest that a gluten-free diet can reduce hypoglycemia in diabetic children with celiac disease, but this has not been shown in adults.[22] One prospective clinical trial of 22 adults with type 1 diabetes and celiac disease demonstrated no significant differences in A1c, insulin dosage, body mass index, or hypoglycemic episodes between those who were following a strict gluten-free diet and those who were not.[22] However, dietary management of celiac disease does improve symptoms, increase weight, and decrease the risk of osteopenia and malignant lymphoma.[22]

>>FAST TRACK<<

Antibody screening should be performed on patients with type 1 diabetes who have possible symptoms of celiac disease.

Lisa began her gluten-free diet with the help of a celiac disease support group Web site. Within two weeks, her headaches, abdominal bloating, diarrhea, canker sores, anxiety, and depression improved. Her serology tests were negative, and

she refused a gastroenterology consultation. Lisa reasoned that her diet, which she had been following for six weeks, had probably resulted in mucosal regeneration of her small bowel. Even if a small-bowel biopsy were negative, she would simply maintain the gluten-free diet on her own. Her glycemic control was improving, and she was beginning to gain weight for the first time in two years. She cancelled her visit to the psychiatrist and updated her primary care physician, who noted the celiac disease Web site with interest as a possible source of support for other patients.

Lisa was able to determine her insulin doses appropriately only after she began to follow a gluten-free diet. Over the past six months, her blood glucose levels have consistently ranged between 74 and 145 mg/dL, and she has not had a single episode of severe hypoglycemia.

MEETING THE CHALLENGE

Managing patients with extreme glycemic variability can be challenging for even the most astute clinicians. Some patients who have been labeled brittle diabetics proudly accept this title because they have stumped so many physicians. But instead of falling prey to this therapeutic trap leading toward management failure, emergency department and urgent care physicians should investigate the likely cause of the patient's glycemic variability. More often than not, the true reason can be uncovered through a thorough interview, a brief physical examination, or a few diagnostic laboratory tests. The cases described above represent just a handful of the multiple etiologies of glycemic variability that taunt diabetologists on a daily basis. Helping these patients find the cause of their brittle state can make a positive impact on their lives for years to come. □

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Correction

In last month's editorial, the airline involved in the accident should have been listed as US Airways.