CME CREDIT ***EDUCATIONAL OBJECTIVE:*** Readers will recognize that ketoacidosis can occur in type 2 diabetes as well as in type 1

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A 48-year-old man with uncontrolled diabetes

A 48-YEAR-OLD WHITE MAN who has had diabetes mellitus for 6 years presents to the outpatient clinic because his blood sugar levels have been rising for the past week.

Both his parents had diabetes, and at the time of his diagnosis he weighed 278 pounds, all of which supported a diagnosis of type 2 diabetes mellitus. His disease was initially managed with diet, exercise, and metformin (Glucophage). Four months later, with weight loss and exercise, his blood sugar levels were consistently under 100 mg/dL, and metformin was discontinued.

He did well until 1 week ago, when he noted polyuria, polydipsia, and rising fingerstick glucose values, higher than 200 mg/dL. He has been eating well, with no nausea, vomiting, or symptoms of dehydration. He denies having any fever, chills, cough, nasal congestion, chest pain, abdominal pain, or dysuria.

In addition to his type 2 diabetes, he has hypertension, for which he takes losartan (Cozaar); hyperlipidemia, for which he takes atorvastatin (Lipitor); and gout, for which he takes allopurinol (Zyloprim).

His blood pressure is 148/70 mm Hg, pulse 100, and weight 273 pounds, and he is afebrile. On examination, his skin, head, eyes, ears, nose, throat, lungs, heart, and abdomen are normal. Urinalysis in the clinic shows large amounts of glucose and ketones.

WHAT IS THE LEAST LIKELY CAUSE OF HIS POOR CONTROL?

1 Which of the following is the least likely cause of his poorly controlled diabetes?

- ☐ Occult infection
- ☐ Poor adherence to diet and exercise
- ☐ Diabetic ketoacidosis
- ☐ Pancreatitis

Until 1 week ago, this patient's diabetes had been well controlled for several years. Pancreatitis is the least likely cause of his uncontrolled diabetes, because he has no history of pancreatitis and has none of the symptoms of acute pancreatitis (fever, vomiting, or severe midepigastric pain radiating into the back).

Poor adherence to medication and lifestyle issues are very common in patients with poorly controlled diabetes and should always be included in the differential diagnosis.

Occult infection should also be considered in a patient with uncontrolled diabetes. Although this patient had no symptoms or signs of infection, urinalysis was done to look for an occult urinary tract infection and, surprisingly, it showed a large amount of ketones.

His diabetes had been well controlled; what has happened?

Case continued: He is treated for diabetic ketoacidosis

Additional testing (TABLE 1) confirms he has a high serum ketone level and acidosis with a high anion gap, consistent with diabetic ketoacidosis. Blood cultures are negative. He is admitted to the hospital and treated with intravenous fluids and an insulin drip at 6 units/hour. Within 48 hours his anion gap normalizes, and he is discharged on a regimen of insulin glargine (Lantus) and insulin lispro (Humalog). A fasting C-peptide level drawn 7 days after his presentation is 1.9 ng/dL (normal 0.8–3.2 ng/dL).

Diabetic ketoacidosis in 'atypical diabetes'

Diabetic ketoacidosis is one of the most seri-

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TABLE 1

The patient's laboratory values

COMPONENT	REFERENCE RANGE	ADMISSION	DAY 1	DAY 2	DAY 7
Glucose	65–100 mg/dL	379	172	268	154
CO_2	23–32 mmol/L	14	13	18	
Anion gap	0–15 mmol/L	22	20	16	
Beta-hydroxybutyrate	0.00–0.30 mmol/L	5.86			
Serum ketones	Negative	Positive			Negative
C-peptide	0.8–3.2 ng/mL				1.9

ous complications of diabetes. Many patients present with nausea, vomiting, and abdominal pain. Dehydration is often present because hyperglycemia leads to glucosuria and volume depletion. Interestingly, our patient showed none of these symptoms or signs.

Diabetic ketoacidosis is increasingly being recognized as a complication in patients with type 2 diabetes mellitus.[1–4] Since the mid-1990s, clinicians have become increasingly aware of a condition variably termed "atypical diabetes," "Flatbush diabetes," "diabetes type 1B," and "ketosis-prone type 2 diabetes mellitus," in which patients, usually obese, present with diabetic ketoacidosis as their first manifestation, but are subsequently found to have type 2 diabetes mellitus. These patients typically are African American or of African, Hispanic, or Caribbean descent.

Ketoacidosis is increasingly being seen in type 2 diabetes

Ketoacidosis results from transient suppression of beta-cell function, the cause of which is unknown. A recent study comparing patients who have type 2 diabetes mellitus with and without diabetic ketoacidosis presenting with decompensated diabetes suggested insulinopenia was the predominant mechanism.[5] For many of these patients, insulinopenia is transient: as the ketoacidosis resolves, beta-cell function improves and, with adequate insulin, lipolysis is reduced.

WHAT CAUSES DIABETIC KETOACIDOSIS?

2 Which of the following hormonal changes underlies the development of diabetic ketoacidosis?

- ☐ Insulin resistance
- ☐ Insulin deficiency
- ☐ Glucagon excess
- ☐ Glucagon deficiency
- ☐ Insulin deficiency and glucagon excess
- ☐ Insulin deficiency and glucagon deficiency

Diabetic ketoacidosis can occur when there is too much glucagon and not enough insulin. Insulin lowers the serum glucose level by promoting glucose uptake in peripheral tissues and by inhibiting gluconeogenesis and glycogenolysis in the liver. Insulin is also anabolic: it inhibits lipolysis in adipocytes and thus decreases the amount of substrate for ketogenesis.

Glucagon is the primary counterregulatory hormone responsible for ketogenesis.[6] In the presence of glucagon excess, malonyl CoA production decreases, causing unblocking of carnitine acyltransferase I (CAT I) and allowing beta-oxidation to occur.[6]

Therefore, the sequence initiating ketogenesis begins with a shift in the ratio of glucagon to insulin, so that there is a relative or absolute excess of glucagon and a deficiency of insulin. A deficiency of insulin accelerates lipolysis, providing more substrate for ketogenesis, while excess glucagon turns on the oxidative sequence for fatty acids in the liver.

Three ketone bodies are produced in diabetic ketoacidosis: two ketoacids (beta-hydroxybutyric acid and acetoacetic acid), and one neutral ketone (acetone). The concentration of insulin required to suppress lipolysis is only one-tenth of that required to promote glucose utilization.[7] Diabetic ketoacidosis is uncommon in patients with type 2 diabetes because they typically have enough insulin to inhibit li-

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polysis (and therefore ketoacid formation) but not enough to promote glucose utilization.

RISK FACTORS FOR DIABETIC KETOACIDOSIS

3 Which of the following is not a risk factor for diabetic ketoacidosis in type 2 diabetes mellitus?

- ☐ Acute illness
- ☐ Age > 65
- ☐ Inadequate insulin doses
- ☐ Antipsychotic drugs
- ☐ Ethnicity

Diabetic ketoacidosis is often precipitated by an acute illness such as an infection, cerebrovascular accident, myocardial infarction, or acute pancreatitis.[8–12] These acute illnesses induce stress in the body and elevate counterregulatory hormones.

Inadequate insulin doses can also lead to diabetic ketoacidosis.

Drugs that affect carbohydrate metabolism are also risk factors. These include glucocorticoids, thiazide diuretics in high doses (> 50 mg daily), sympathomimetic agents, and second-generation antipsychotic agents (also called "atypical" antipsychotics) such as clozapine (Clozaril) and olanzapine (Zyprexa), although some are worse than others.[13,14]

Ketosis-prone type 2 diabetes mellitus is more prevalent in African Americans and Hispanics.[8,15,16]

Age is not a risk factor for developing diabetic ketoacidosis. In fact, diabetic ketoacidosis is the leading cause of morbidity and death in children with type 1 diabetes and can also occur in children with type 2 diabetes, particularly in obese African American adolescents.[2]

DISTINGUISHING TYPE 1 FROM TYPE 2

4 Which of the following is most specific in distinguishing type 1 from type 2 diabetes mellitus?

- ☐ C-peptide levels
- ☐ Islet cell antibodies
- ☐ Body mass index
- ☐ Family history
- ☐ Hemoglobin A_{1c} level

Type 1 diabetes is characterized by destruction of pancreatic beta cells, leading to absolute insulin deficiency. The process is usually mediated by autoimmunity; therefore, testing for antibodies to islet cells, glutamic acid decarboxylase, insulin, and tyrosine phosphatase is the most specific way to distinguish type 1 from type 2 diabetes mellitus.

The hemoglobin A_{1c} level correlates with the mean blood glucose level over the previous 8 to 12 weeks. The hemoglobin A_{1c} is typically elevated in both type 1 and type 2 diabetes mellitus and therefore is not a useful distinguishing feature.

C-peptide is made when proinsulin is cleaved into insulin and C-peptide. It is released from endocytic vesicles with insulin in a one-to-one molar ratio. Thus, the level of C-peptide in the blood can show how much insulin is being made by the pancreas. C-peptide levels can help distinguish between type 1 and type 2 diabetes mellitus later in the course of the disease (levels are usually lower in a patient with type 1 diabetes), but they are not as useful early on because they can be normal early in the course of type 1 diabetes.[17]

A family history of diabetes is more common in type 2 diabetes, but patients with either type 1 or type 2 can have an affected close relative.

Less insulin is needed to suppress lipolysis than to promote glucose use

Patients with type 2 diabetes are generally overweight, with a body mass index greater than the 85th percentile for their age and sex. In contrast, patients with type 1 diabetes are usually not overweight and often have a recent history of weight loss. There are exceptions, however, and some patients with type 1 diabetes have an elevated body mass index, while some patients with type 2 diabetes are thin.

Although individually, C-peptide, family history, and body mass index are not very specific in distinguishing type 1 from type 2 diabetes mellitus, together they often give the clinician a good idea of the type of diabetes the patient has. In our case, although islet cell antibodies were not drawn, the normal C-peptide level, high body mass index, and family history all support a diagnosis of type 2 diabetes mellitus.

THE PATIENT CONTINUES TO DO WELL

The patient is discharged from the hospital on an insulin regimen. His blood sugar levels are

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closely monitored and remain near normal. Six months after the episode of diabetic ketoacidosis, his insulin is discontinued.

TAKE-HOME POINTS

Diabetic ketoacidosis is not unique to type 1 diabetes mellitus. It can occur in type 2, more commonly in patients who are nonwhite and who have precipitating factors such as acute illness, inadequate insulin treatment, or newly diagnosed diabetes. Clinicians should be aware of the possibility of diabetic ketoacidosis even in patients with type 2 diabetes who may not have these risk factors.

One approach to recognizing diabetic ketoacidosis better in patients with type 2 diabetes mellitus would include checking urine for ketones and serum electrolytes for high anion gap acidosis when patients with type 2 diabetes present with uncontrolled blood sugar levels. If ketonuria or acidosis is present, serum ketone and beta-hydroxybutyrate levels should be obtained to evaluate for diabetic ketoacidosis.

Patients should take insulin for an indeterminate period of time after initial treatment of diabetic ketoacidosis. As our case illustrates, in many cases, beta-cell function will return sufficiently to allow insulin to be discontinued. There are no clear guidelines for how long to continue insulin, but most practitioners continue it for weeks to months and discontinue it when glucose levels are stable and remain so with tapering doses. Sometimes oral agents need to be added as insulin is tapered.

Insulin therapy is tailored to the individual patient on the basis of blood glucose values. There are no data on which type of insulin is the most effective, and there are no data on whether these patients are at greater risk of hypoglycemia than other patients taking insulin. In general, there is no evidence that "prophylactic" insulin (ie, giving insulin to prevent diabetic ketoacidosis during times of illness or stress) is required. However, blood glucose monitoring is appropriate during infection or stress, and if hyperglycemia occurs in these situations, insulin use is prudent to reduce the risks of recurrent diabetic ketoacidosis.

No data yet on how long to continue insulin after an episode of diabetic ketoacidosis

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