Ketogenic Diet as a Trigger for Diabetic Ketoacidosis in a Misdiagnosis of Diabetes: A Case Report

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Case Presentation

A 30-year-old Caucasian man with a 2-month history of type 2 diabetes presented to the emergency department with abdominal pain, emesis with occasional coffee-ground content, and constipation of 6 days' duration. The day before, he had presented to an urgent care center for similar complaints and was told he had a high stool burden and was prescribed an oral laxative, which he was unable to tolerate.

He was taking metformin 1,000 mg twice daily for type 2 diabetes and had also initiated lifestyle modifications, which included an intensive low-carbohydrate ketogenic diet. He had restricted his carbohydrate intake to no more than 20 g/day. His family history included type 2 diabetes in his father and type 1 diabetes in a grandparent. He reported having lost 60 lb during the past 2 months, and his current weight was 263 lb (BMI 33.5 kg/m^2). Previous lipid panels were only significant for low HDL cholesterol of 33 mg/dL. Since his diabetes diagnosis, home monitoring had revealed blood glucose fluctuations between 90 and 400 mg/dL despite changes in activity and diet and initiation of medication.

His vital signs included blood pressure 159/100 mmHg, pulse 98 bpm, respiration rate 26/minutes with noted Kussmaul breathing, oxygen saturation 99%, and temperature 98.1°F. Physical examination revealed diffuse abdominal tenderness, dry mucous membranes, and an acetone-like scent on his breath. Further testing revealed the results shown in Table 1, which included positive urine ketones and glucose, elevated serum ketones, a pH of 6.97, an elevated anion gap, and a blood glucose of 424 mg/dL. A diagnosis of diabetic ketoacidosis (DKA) was established, and the patient was admitted to the intensive care unit and started on treatment with intravenous fluids, insulin, potassium, and pantoprazole.

Surgery was consulted to rule out a possible gastrointestinal bleed. Esophagogastroduodenoscopy was performed and revealed mild gastritis but no signs of an acute bleed. Additionally, gastric antral biopsy was negative for *Helicobacter pylori*. During the next 24 hours, the patient's acidemia, hyperglycemia, and ketosis improved. The diabetes service was consulted for DKA and diabetes management. The diabetes service suspected type 1 diabetes despite the patient's previous diagnosis of type 2 diabetes. Laboratory results included an elevated A1C of 8.5%, a low C-peptide level, elevated GAD65 antibodies, and elevated zinc transporter 8 antibodies (Table 2), all suggesting type 1 rather than type 2 diabetes.

He was given the diagnosis of type 1 diabetes, possibly latent autoimmune diabetes in adults (LADA), discharged from the hospital, and started on insulin glargine and lispro.

Questions

1. What are the risks and contraindications regarding patients initiating a low-carbohydrate ketogenic diet?
2. Should the diagnosis of type 1 diabetes or LADA be excluded before patients with an atypical presentation of type 2 diabetes or those with other autoimmune disorders who have been diagnosed with type 2 diabetes begin an intensive low-carbohydrate diet?
3. What are the distinguishing hallmarks of nutritional ketosis compared with ketoacidosis?

Commentary

LADA is defined as a mixed disease combining aspects of the clinical phenotype and pathophysiology of type 1 and

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TABLE 1 Patient's Laboratory Test Results at Initial Presentation

Test	Value (Normal Range)
Sodium, mmol/L	136 (135–145)
Potassium, mmol/L	4.7 (3.5–5.1)
Chloride, mmol/L	104 (98–108)
Bicarbonate, mmol/L	6 (21–32)
Blood urea nitrogen, mg/dL	11 (8–25)
Glucose, mg/dL	424 (66–99)
Creatinine, mg/dL	1.64 (0.50–1.30)
Calcium, mg/dL	9.2 (8.4–10.2)
Anion gap, mmol/L	30.7 (10.0–20.0)
β-Hydroxybutyrate, mmol/L	>8.00 (0.02–0.27)
Lactic acid, mmol/L	2.7 (0.6–2.0)
Venous pH	6.97 (7.32–7.42)
Venous partial pressure of carbon dioxide	15.6 (41.0–51.0)
Venous base excess, mmol/L	−26.8 (−2.0 to 2.0)
Osmolality, mOsm/kg	328 (275–295)

type 2 diabetes. Patients with LADA, while initially insulin independent, test positive for many of the same islet cell autoantibodies found in type 1 diabetes but have clinical features such as older age, higher BMI, and insidious onset, which more resemble features of type 2 diabetes. Many of those diagnosed with LADA become insulin dependent about 6–12 months after their diagnosis with diabetes. Because of this, LADA often goes unnoticed and has a high misdiagnosis rate of 5–10% of people thought to have type 2 diabetes (1).

Despite becoming insulin dependent within 2 months of diagnosis, the patient in this case had other criteria for a LADA diagnosis, including an age ≥30 years and having tested positive for antibodies. Had he not presented in DKA, typical care likely would have started with initiation of oral agents with the eventual addition of insulin with time (2). Ketosis-prone type 2 diabetes was also a possible differential for this patient, but given the positive antibodies and the fact that ketosis-prone type 2 diabetes is more common in Hispanic and African-American patients, this diagnosis seemed less likely (3). In our case, the misdiagnosis of LADA combined with a very strict ketogenic diet culminated in the acute presentation of DKA just 2 months after the patient's initial diabetes diagnosis.

TABLE 2 Patient's Diabetes and Antibody Testing Results

Test	Value (Normal Range)
A1C, %	8.5 (4.0–5.6)
C-peptide, ng/mL	0.42 (0.90–5.00)
GAD65 antibodies, nmol/L	195 (≤ 0.02)
Insulin antibodies, nmol/L	0.02 (0.00–0.02)
Zinc transporter 8 antibodies, U/mL	229 (<15.0)

A ketogenic diet is a high-fat, adequate-protein, and very-low-carbohydrate eating pattern that leads to nutritional ketosis. Because of the low intake of carbohydrates, glycolysis activity falls to very low levels, thus reducing the amount of oxaloacetate available in the citric acid cycle. Consequently, oxaloacetate is not available to combine with acetyl coenzyme A (acetyl-CoA), which results from the breakdown of fatty acids. This situation causes shunting of acetyl-CoA to ketogenesis and results in the formation of ketone bodies that include β-hydroxybutyrate, acetoacetate, and acetone (4,5). These ketone bodies can be used, to some extent, as a fuel source for brain, heart, and muscle tissue when glucose is not available and glycogen stores are depleted. In the context of dietary ketosis, ketone body levels can be elevated in the range of 1–3 mmol/L compared with up to 10 mmol/L in ketoacidosis. As a result of low carbohydrate intake, insulin release also decreases (5,6).

Contrasting nutritional ketosis with ketoacidosis, DKA results from absolute insulin deficiency, resulting in an unopposed increase in counterregulatory hormones such as glucagon. This insulin deficiency and glucagon surplus results in unopposed gluconeogenesis by the liver. The resulting elevated glucose levels are unable to be used by surrounding tissues because of a lack of insulin. This, in turn, results in the body resorting to lipid breakdown and amino acid catabolism to meet the energy needs of peripheral tissues, the former resulting in the formation of ketone bodies. The formation and accumulation of these ketone bodies significantly outpaces renal excretion, resulting in a metabolic acidosis (4–6).

The patient reported in our case had an insulin deficiency resulting from autoimmune attack of the β-cells of the pancreas. This insulin deficiency, combined with a strict ketogenic diet of <20 g net carbohydrates per day culminated in an acute presentation of DKA. It is possible that the resulting physiological ketosis acted as a trigger for the onset of DKA by reducing insulin output by the pancreas via a low-carbohydrate diet and increasing basal levels of ketone bodies to subclinical DKA levels. As the patient's islet cell mass decreased over time from autoimmune destruction, insulin levels decreased as well, resulting in an accelerated presentation of DKA.

Potential clinical uses of a ketogenic diet as part of medical treatment plans have been gaining traction in recent years. The greatest body of evidence for the benefit of a ketogenic diet exists in those with refractory epilepsy (4). The evidence of benefit with regard to a ketogenic diet in individuals diagnosed with type 2 diabetes is also well established and includes improved glycemic control, reduced diabetes medication needs, increased HDL cholesterol levels, greater weight loss, and reversal of diabetic nephropathy (4).

However, nutritional ketosis must be contrasted with carbohydrate restriction. A ketogenic diet is defined as featuring carbohydrate restriction to <20 g/day, compared with current American Diabetes Association (ADA) guidelines regarding carbohydrate restriction to no more than 60 g/meal for females or 75 g/meal for males. These restrictions are based on the ADA's Standards of Care recommendations of a diet of 1,500 kcal/day for females or 1,800 kcal/day for males, with no more than 45% of calories from carbohydrates (7).

The risks of a ketogenic diet in insulin-deficient individuals are not well described. It should be noted that individuals with type 2 diabetes who are taking a sodium–glucose cotransporter 2 (SGLT2) inhibitor are at an increased risk of euglycemic DKA when following a low-carbohydrate ketogenic diet (4,8,9). Additionally, a ketogenic diet should not be initiated in individuals with certain hereditary defects of fat metabolism or certain enzyme deficiencies (4). Cases have also been reported of ketoacidosis occurring in individuals without a diagnosis of diabetes who were following a low-carbohydrate ketogenic diet. Although one of these cases was attributed to lactation, this type of diet is increasingly a potential differential for the etiology of metabolic acidosis (10,11).

Clinical Pearls

- Screening for autoimmune diabetes or insulin deficiency should be considered in patients with an atypical history of type 2 diabetes who are starting a ketogenic diet.
- Ketogenic diets are increasingly implicated in ketoacidosis in both individuals with and without diabetes.
- SGLT2 inhibitors should be avoided in individuals following a ketogenic diet.
- More research is needed into the potential risks and contraindications of a ketogenic diet as this diet gains popularity in the United States.

DUALITY OF INTEREST

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

AUTHOR CONTRIBUTIONS

A.J.W.-C. performed a literature review and wrote the manuscript. A.M.H. treated the patient described in this case, contributed to the manuscript, and reviewed/edited the manuscript. A.M.H. is the guarantor of this work and, as such, ensures the veracity of the case study and the details of the presentation.

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