



# A Case of Euglycemic Diabetic Ketoacidosis Triggered by a Ketogenic Diet in a Patient With Type 2 Diabetes Using a Sodium–Glucose Cotransporter 2 Inhibitor

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Sodium–glucose cotransporter 2 (SGLT2) inhibitors are one of the newest classes of antihyperglycemic medications now available for the treatment of type 2 diabetes (1). Clinical guidelines recommend this type of medication as one of various possible approaches for pharmacological therapy after failure of or intolerance to metformin (1).

SGLT2 inhibitors are the first class of medications that act on the kidneys to optimize glycemic control; they prevent the reabsorption of glucose in the proximal renal tubules by targeting the action of the protein SGLT2 (2). As glucose is excreted through the urine, plasma glucose levels fall, leading to an improvement in glycemia (1).

The most common adverse side effects attributed to SGLT2 inhibitors are genital and urinary infections. Because of osmotic diuresis induced by the glucosuria resulting from SGLT2 inhibition, volume depletion is also a possibility (3). Recently, episodes of diabetic ketoacidosis (DKA) have been identified as a rare side effect (2).

As a consequence of the glucosuria induced by SGLT2 inhibition, the majority of reported DKA episodes have been associated with a mild to moderate increased glycemia (4).

## Case Presentation

R.F., a 44-year-old man with a history of type 2 diabetes, presented to the hospital emergency department with complaints of malaise, fatigue, heartburn, and decreased exercise capacity. He had been taking the dipeptidyl peptidase 4 inhibitor sitagliptin 100 mg, the SGLT2 inhibitor empagliflozin 25 mg, and metformin 1,000 mg twice daily for the past 2 years. He said his symptoms started 4 days earlier. The only change he could identify in his lifestyle was that he had switched to a ketogenic diet and was restricting carbohydrates, which he had been doing for 7 days before coming to the hospital.

R.F.'s heart rate was 120 bpm, his blood pressure was 120/80 mmHg, and his temperature was 97.8°F. On physical exam, he was found to be uncomfortable and in mild distress, and he exhibited tenderness to palpation over the epigastric area. Initial laboratory test values were sodium 132 mmol/L (normal 134–148), potassium 5.5 mmol/L (normal 3.5–5.5), serum bicarbonate 9 mmol/L (normal 22–32), anion gap 24 mmol/L (normal 7–14), serum glucose 199 mmol/L (normal 70–100), and  $\beta$ -hydroxybutyrate 8.89 mmol/L (normal 0.02–0.27). Urine tests revealed ketones 150 mg/dL (normal negative) and urine glucose 1,000 mmol/L (normal negative). Arterial blood gases taken on 2 L of oxygen supplementation by nasal cannula were significant for a pH 7.11 (normal 7.35–7.45), partial pressure of carbon dioxide <19 mmHg (normal 35–45), partial pressure of oxygen 105 mmHg (normal 80–100), and bicarbonate 8.2 mmol/L (normal 22–26).

R.F.'s acidosis was thought to be the result of euglycemic DKA, likely triggered by his ketogenic diet; other etiologies, including infection and lactic acidosis secondary to metformin use, were ruled out with further testing, which revealed a lactic acid level of 1.8 mmol/L (normal 0–2), an ethanol level <10 mg/dL, and a negative salicylate level. Chest X-ray showed no signs of pneumonia, and results of a urinalysis were unremarkable.

R.F. was admitted to the intensive care unit for suspicion of euglycemic DKA. He was started on an insulin drip and intravenous (IV) fluids per DKA protocol. The main difference in therapy for euglycemic DKA versus ordinary DKA was the type of IV fluids provided and the insulin

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dosage administered. Based on his blood glucose level, he was started on D5/0.45% sodium chloride with 20 mEq potassium chloride at 250 mL/hour instead of normal saline. The initial standard regular insulin dosage of the drip was decreased from 0.14 to 0.07 units/kg/hour based on glycemia. No additional potassium supplementation was required based on his admission potassium level.

The patient was kept on an insulin drip for 16 hours while progressively decreasing the IV fluids rate and monitoring blood glucose hourly to avoid hypoglycemia. Once his bicarbonate level was  $>18$  mmol/L and the anion gap had closed, he was transitioned to weight-based basal and premeal insulin and then transferred to the medical floor.

At discharge, it was recommended that he continue on metformin and sitagliptin and discontinue empagliflozin. He was encouraged to follow up with endocrinology as an outpatient.

## Questions

1. What is the relationship between SGLT2 inhibitors and euglycemic DKA?
2. What are the precipitating factors for euglycemic DKA with the use of an SGLT2 inhibitor?
3. What are the potential mechanisms by which the combination of an SGLT2 inhibitor and a ketogenic diet can cause euglycemic DKA?
4. What considerations are specific to the management of euglycemic DKA induced by an SGLT2 inhibitor?

## Commentary

DKA is a severe complication of diabetes that can be lethal (2). It can result from a severe lack of insulin action in the body (2). It can be defined as a triad that includes metabolic acidosis, hyperglycemia, and increased ketone bodies in the blood and urine; however, it can also be seen in the setting of normal or slightly elevated glycemia (2,5). This latter form of DKA is known as euglycemic or normoglycemic DKA and was initially characterized by blood glucose values  $<300$  mg/dL. In 2015, the American Association of Clinical Endocrinologists and the American College of Endocrinology recommended calling this form of DKA “DKA with lower-than-anticipated levels of glucose” instead of “euglycemic DKA,” because the majority of 80 DKA cases reviewed were found to have a blood glucose level  $>250$  mg/dL (6).

In May 2015, the U.S. Food and Drug Administration (FDA) issued a warning regarding the risk of DKA with the use of SGLT2 inhibitors. The FDA performed a review of

its system database from March 2013 to May 2015 and identified 73 reported cases of DKA in patients treated with SGLT2 inhibitors. The warning mentioned that, in many of these cases, DKA was not immediately recognized because of the presence of low to normal blood glucose levels (7). All SGLT2 inhibitors currently approved by the FDA for the management of type 2 diabetes have been associated with DKA, leading the FDA to require a warning on their package labels (7,8).

Burke et al. (9) performed a systematic review investigating the relationship between SGLT2 inhibitors and DKA in patients with diabetes. They found 34 case reports of patients with type 1 or type 2 diabetes who developed DKA while receiving an SGLT2 inhibitor. Of these cases, 26 involved canagliflozin, 5 involved dapagliflozin, 2 involved empagliflozin, and 1 involved ipragliflozin, which is an SGLT2 inhibitor approved in Japan (9).

Similar to our patient, the two cases involving empagliflozin that were previously described in the literature presented as euglycemic DKA. One case was reported in a 64-year-old woman with type 2 diabetes using the glucagon-like peptide 1 receptor agonist liraglutide, who developed DKA 5 days after initiating empagliflozin (10). The second case was in a 53-year-old man with type 2 diabetes who was admitted to the hospital with acute pancreatitis; he had been taking empagliflozin for 3 years and was found to have euglycemic DKA (11).

Metabolic stress has been the unifying theme among the reported cases of DKA involving SGLT2 inhibitors (7,9). SGLT2 inhibitors are thought to increase the risk of euglycemic DKA by two potential mechanisms. The first is an increase in urinary glucose excretion, which in turn leads to a decrease in glycemic levels, resulting in the reduction of endogenous insulin secretion and increased production of free fatty acids (FFAs), which are later converted into ketone bodies (6,9). The second mechanism is the decrease in blood glucose levels induced by SGLT2 inhibition, which leads to reduced insulin production from pancreatic  $\beta$ -cells and increased stimulation of  $\alpha$ -cells, which in turn increases plasma glucagon concentrations (9). In addition, SGLT2 inhibitors act independently on pancreatic  $\alpha$ -cells, promoting an increase in plasma glucagon levels (9,12).

The two mechanisms described above cause a decrease in the insulin-to-glucagon ratio, which stimulates lipolysis, augmenting delivery of FFAs to the liver and resulting in mild stimulation of ketogenesis. If insulin deficiency is more profound, as can happen in patients with type 1 diabetes, or if carbohydrate availability is drastically

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restricted, as with adherence to a ketogenic diet, this mild ketosis can evolve into DKA (12).

The unique presentation of euglycemic DKA induced by SGLT2 inhibitors makes both its diagnosis and management challenging. At presentation, patients may be normoglycemic, so health care providers should carefully consider which type of IV fluids should be given based on serum potassium levels and glycemia (13). Relatively lower amounts of IV insulin should be initiated to avoid hypoglycemia. It has also been observed that low to normal serum potassium levels may be present, and patients might require earlier replacement (13).

Several risk factors have been associated with the development of DKA with SGLT2 inhibitor use. These include a decrease in insulin or secretagogue dose, starvation or decrease in carbohydrate intake, acute illness, pregnancy, and alcohol intake (14).

A change in diet, notably decreased carbohydrate intake, shifts metabolism to the use of fat for energy, which promotes ketone production and may contribute to the eventual development of DKA under stressful conditions (6). The ketogenic diet is characterized by a reduction in carbohydrate intake (usually to <50 g/day) while maintaining a sufficient protein intake and consuming >70% of daily calories from fatty foods (15,16).

Although the ketogenic diet has become popular as a weight loss approach, its long-term side effects and sustainability have yet to be studied in depth. In the case of patients with type 2 diabetes who are under treatment with an SGLT2 inhibitor, it is contraindicated because it can cause euglycemic DKA (12,17).

### Clinical Pearls

- Euglycemic DKA is an underdiagnosed medical emergency that can develop in patients who are taking an SGLT2 inhibitor. A nonspecific clinical presentation and near-normal blood glucose levels are likely the main reasons this diagnosis is often missed.
- The interaction between diet and SGLT2 inhibition has not been fully studied. It is particularly important to note new side effects in patients who have started a ketogenic diet while on one of these medications.
- Given the difficulty of diagnosing this syndrome, we encourage health care providers prescribing these medications to counsel their patients about possible complications and side effects.
- By understanding the etiology and precipitating factors of DKA with the use of SGLT2 inhibitors, clinicians can take the necessary precautions to reduce such events.

- We recommend that patients with type 2 diabetes avoid changing their diet without consulting a physician or dietitian.

### DUALITY OF INTEREST

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

### AUTHOR CONTRIBUTIONS

P.S.G. and G.Z. researched the data and wrote the manuscript. R.L. reviewed and edited the manuscript. P.S.G. is the guarantor of this work and, as such, had full access to all the data presented and takes responsibility for the integrity of the data and the accuracy of the case report.

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