Euglycemic Diabetic Ketoacidosis in a Patient Prescribed Empagliflozin and a Ketogenic Diet: A Case of Misdiagnosed Type 1 Diabetes

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Background

Diabetic ketoacidosis (DKA) is defined as a biochemical triad of hyperglycemia (blood glucose >250 mg/dL), ketonemia/ketonuria, and high anion-gap metabolic acidosis (AGMA). Although hyperglycemia is a distinct characteristic in DKA (1), a euglycemic DKA (EDKA) variant exists in which a patient's blood glucose is normal or mildly elevated on presentation.

Sodium–glucose cotransporter 2 (SGLT2) inhibitors such as empagliflozin and dapagliflozin, approved by the U.S. Food and Drug Administration (FDA) for the treatment of type 2 diabetes, have been reported to increase the risk of EDKA, especially in patients with type 1 diabetes (2).

We present a unique case of EDKA associated with SGLT2 inhibitor use that was complicated by ketosis induced by a ketogenic diet and unmasking underlying type 1 diabetes in a patient previously treated as having type 2 diabetes.

Case Presentation

A 70-year-old Caucasian woman with a medical history significant for type 2 diabetes and hypothyroidism presented to the emergency department (ED) with shortness of breath and dizziness for 4 days, associated with one episode of nausea and vomiting. On presentation, she had normal vital signs except for tachycardia. The remainder of her physical exam was unremarkable. Her BMI was 21.8 kg/m^2. Her initial diagnostic work-up is summarized in Table 1.

Six months before her presentation, the patient relocated and began receiving primary care in our health system. Before that time, her diabetes was comanaged by a different primary care provider and an endocrinologist. Oral agents had not adequately controlled her blood glucose, and she had been transitioned to insulin.

On initial evaluation in our health system, her diabetes was inadequately controlled (as reflected by an A1C of 8.7%) with long-acting subcutaneous insulin glargine 10 units daily and correctional regular insulin on a sliding scale. During her follow-up visits, she reported frequent episodes of early-morning hypoglycemia (blood glucose 30–60s mg/dL). As a result, metformin was added to her regimen, and sliding-scale insulin was discontinued.

One month before her admission, her A1C had increased to 8.9%. At that time, empagliflozin was added to her regimen, while her insulin and metformin doses remained the same. Along the same timeline, she also started following a strict ketogenic diet, with meals consisting mainly of protein and an occasional salad.

She was admitted to the hospital for management of high anion gap metabolic acidosis associated with ketosis. Because her blood glucose was not elevated, the ketosis was initially thought to be caused solely by the ketogenic diet. However, consideration was given to the known potential for empagliflozin to cause EDKA. She was treated with a modified version of the institution's DKA protocol. Dextrose-containing maintenance intravenous (IV) fluids were initiated, and the usual IV insulin infusion was held until her blood glucose increased to >250 mg/dL. The insulin infusion was initiated at half of the usual weight-based dose for DKA treatment (i.e., 0.05 units/kg/hour). The insulin infusion and dextrose-containing maintenance fluids were titrated per an institutional nomogram to maintain a blood glucose of 200–250 mg/dL. Both metformin and empagliflozin were held during this period. Her AGMA resolved after ~36 hours of therapy. After resolution of EKDA/AGMA, subcutaneous

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TABLE 1 Laboratory Values on Presentation and Associated Reference Ranges

	Measured Value	Reference Range
Sodium, mEq/L	139	135–145
Potassium, mEq/L	4.1	3.5–5
Chloride, mEq/L	102	98–108
Creatinine, mg/dL	0.8	0.5–1.2
BUN, mg/dL	25	7–17
Carbon dioxide, mmol/L	10	23–32
Glucose, mg/dL	136	65–99
Anion gap, mEq/L	27	5–15
β-Hydroxybutyrate, mmol/L	8.8	0.02–0.27
VBG pH	7.154	7.32–7.42
VBG pCO_2, mmHg	27.8	41–51
VBG pO_2, mmHg	22.6	25–40
Lactic acid, mmol/L	1	0.7–2.1
Ethanol, mg/dL	< 10	0–50
Salicylates, mg/dL	< 3	50–300
Ethylene glycol, μg/mL	< 10	≤10
A1C, %	9	<5.7

BUN, blood urea nitrogen; pCO_2, partial pressure of carbon dioxide; pO_2, partial pressure of oxygen; VBG, venous blood gas.

insulin therapy was initiated. Because of the associated risks of EDKA in patients with type 1 diabetes treated with SGLT2 inhibitors, it was suspected that the patient may in fact have type 1 diabetes. A GAD antibody test was sent, which came back positive, thus confirming the diagnosis of type 1 diabetes. She was eventually discharged home with basal-bolus insulin therapy and was instructed to discontinue empagliflozin and metformin.

Questions

- Can the ketogenic diet increase the likelihood of EDKA in patients treated with SGLT2 inhibitors?
- Is the ketogenic diet safe in patients with type 1 diabetes?
- Should SGLT2 inhibitors be considered contraindicated in patients with type 1 diabetes?

Commentary

SGLT2 inhibitors work by blocking glucose reabsorption and promoting glycosuria in the proximal tubules of the nephron. Because of their noninsulin-dependent mechanism, and thus their low risk for causing hypoglycemia and weight gain, there has been an interest in using SGLT2 inhibitors off label to treat patients with type 1 diabetes (2). However, there have been reports of EDKA associated with SGLT2 inhibitors, particularly when used in type 1 diabetes (2–5). These reports have led to warnings from the FDA and others regarding SGLT2 inhibitors causing ketoacidosis (6).

The mechanism of action of EDKA associated with SGLT2 inhibitors is unclear but thought to be the result of increased excretion of glucose via the urine and lowering of serum glucose, thus leading to decreased insulin secretion and decreased tissue uptake of glucose as an energy source. Additionally, SGLT2 inhibitors may directly stimulate α-cells of the pancreas and cause release of glucagon, which further promotes lipolysis and ketogenesis (2,7,8). Starvation ketosis shares a similar mechanism, which can occur even in healthy individuals without diabetes (2). This effect is often described as the goal of the ketogenic diet: to take in minimal carbohydrates so the body must metabolize its own fat stores for energy, thus leading to weight loss. However, the ketogenic diet can also put a person with diabetes at risk for developing ketoacidosis because of an absolute or relative insulin deficiency (3). In people without diabetes, the risk is less pronounced because starvation ketosis usually leads to a very mild (if present) acidosis, resulting from several cellular braking mechanisms that prevent the overt buildup of ketone bodies. These mechanisms include an increased utilization of ketoacids in the central nervous system and peripheral tissues, as well as modulation of insulin and glucagon secretion. The net effect leads to a rate of hepatic ketone production that matches or slightly exceeds ketone utilization (9).

DKA occurs more commonly in type 1 diabetes because of an absolute insulin deficiency (3). In our patient, a misdiagnosis of type 2 diabetes led to an insulin underutilization because of euglycemia, giving the appearance of appropriately managed type 2 diabetes but masking the development of a more insidious disease process. This case is notable because our patient had multiple factors that contributed to the development of ketosis/EDKA in the setting of misdiagnosed type 2 diabetes. Importantly, no evaluation for type 1 diabetes had occurred in our patient before the prescription of an SGLT2 inhibitor. In adults, new-onset type 1 diabetes (i.e., latent autoimmune diabetes in adults) is often mistaken for type 2 diabetes (10).

Our patient's EDKA took 36 hours to resolve, which is a stark increase from previously reported median time to resolution of 11 hours (11). It was important to start dextrose-containing fluids first not only to prevent hypoglycemia, but also to help halt the disease process by giving energy substrate to be taken up by tissues when insulin was eventually introduced. The modified protocol was safe and effective, with no hypoglycemic events despite presenting with euglycemia.

To conclude, we report here a unique case of EDKA associated with empagliflozin that was initially overlooked as starvation ketoacidosis resulting from the ketogenic diet. Further work revealed a patient with type 1 diabetes who was being treated with oral agents indicated for type 2 diabetes, all of which may have contributed to and precipitated EDKA. This case highlights the importance of accurately diagnosing diabetes subclasses and emphasizes the need to consider dietary risk factors in addition to medications when managing this subclass of diabetes.

Clinical Pearls

- DKA should be considered in the differential diagnosis for patients with high anion gap metabolic acidosis taking an SGLT2 inhibitor, even if other potential causes are present.
- The ketogenic diet may need to be prescribed cautiously in patients receiving SGLT2 inhibitors or with other risk factors for DKA until more safety information is available.
- Appropriate patient selection and assessment of risk factors, including type 1 diabetes, are essential for the safe prescribing of SGLT2 inhibitors and prevention of DKA.

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DUALITY OF INTEREST

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

AUTHOR CONTRIBUTIONS

All authors contributed to background and analysis of this case report. A.L.H. and X.Q.Y. wrote the manuscript. S.S.K., A.J.F, and D.U. reviewed/edited the manuscript. A.L.H. is the guarantor of this work and, as such, had full access to all the data in this report and takes responsibility for the integrity and accuracy of the information reported.

REFERENCES

1. Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. Diabetes Care 2009; 32:1335–1343

2. Danne T, Garg S, Peters AL, et al. International consensus on risk management of diabetic ketoacidosis in patients with type 1 diabetes treated with sodium–glucose cotransporter (SGLT) inhibitors. Diabetes Care 2019;42:1147–1154

3. Nyenwe EA, Kitabchi AE. The evolution of diabetic ketoacidosis: an update of its etiology, pathogenesis and management. Metabolism 2016;65:507–521

4. Blau JE, Tella SH, Taylor SI, Rother KI. Ketoacidosis associated with SGLT2 inhibitor treatment: analysis of FAERS data. Diabetes Metab Res Rev 2017;33 (DOI: 10.1002/dmrr.2924)

5. Peters AL, Buschur EO, Buse JB, Cohan P, Diner JC, Hirsch IB. Euglycemic diabetic ketoacidosis: a potential complication of treatment with sodium–glucose cotransporter 2 inhibition. Diabetes Care 2015;38:1687–1693

6. U.S. Food and Drug Administration. FDA drug safety communication: FDA revises labels of SGLT2 inhibitors for diabetes to include warnings about too much acid in the blood and serious urinary tract infections. Available from https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-revises-labels-sglt2-inhibitors-diabetes-include-warnings-about. Accessed 10 November 2019

7. Diaz-Ramos A, Eilbert W, Marquez D. Euglycemic diabetic ketoacidosis associated with sodium-glucose cotransporter-2 inhibitor use: a case report and review of the literature. Int J Emerg Med 2019;12:27

8. Ogawa W, Sakaguchi K. Euglycemic diabetic ketoacidosis induced by SGLT2 inhibitors: possible mechanism and contributing factors. J Diabetes Investig 2016;7:135–138

9. Basnet S, Tachamo N, Nazir S, Dhital R, Jehangir A, Donato A. Severe anion gap metabolic acidosis associated with initiation of a very low-carbohydrate diet. J Community Hosp Intern Med Perspect 2019;9:165–167

10. O'Neal KS, Johnson JL, Panak RL. Recognizing and appropriately treating latent autoimmune diabetes in adults. Diabetes Spectr 2016;29:249–252

11. Tran TTT, Pease A, Wood AJ, et al. Review of evidence for adult diabetic ketoacidosis management protocols. Front Endocrinol (Lausanne) 2017;8:106