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REVIEW ARTICLE

Fasting-Associated Euglycemic Diabetic Ketoacidosis in a Patient on SGLT2 Inhibitor Therapy: A Rare and Challenging Diagnostic Dilemma in the Emergency Department

Vijay Kumar S.S.[1], Ananth Prasad Rao H.T.[2], Shabbir Shekhli[3], Anila Jose[4]

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ABSTRACT

Euglycemic diabetic ketoacidosis (eDKA) is a rare but life-threatening condition that can occur in patients taking sodium-glucose cotransporter 2 (SGLT2) inhibitors, particularly under conditions of metabolic stress, such as fasting. We report the case of a 45-year-old male with type 2 diabetes who presented to the emergency department with symptoms of nausea, vomiting, and tachypnea following prolonged fasting during a religious observance. Despite normal blood glucose levels, he was diagnosed with eDKA, likely triggered by the combined effects of fasting and SGLT2 inhibitor therapy. This case underscores the importance of considering eDKA in patients on SGLT2 inhibitors, even with normal glucose levels, particularly during periods of fasting or metabolic stress. The management of eDKA follows the principles of traditional diabetic ketoacidosis treatment, including insulin infusion, fluid resuscitation, and electrolyte correction. Awareness of this rare complication is crucial for emergency physicians to ensure timely diagnosis and intervention.

KEYWORDS

Euglycemic Diabetic Ketoacidosis (eDKA), SGLT2 Inhibitors, Fasting, Emergency Department

AUTHOR'S AFFILIATION:

[1] Assistant Profesor, Department of Emergency Medicine, Kanachur Institute of Medical Sciences, Deralakatte, Mangalore 575018, India.

[2] Associate Professor, Department of Emergency Medicine, Kanachur Institute of Medical Sciences, Mangalore 575018, India.

[3] Associate Professor, Department of Emergency Medicine, Rajarajeshwari Medical College and Hospital, Bangalore 560074, India.

[4] Assistant Professor, Department of General Medicine, Sree Narayana Institute of Medical Sciences Chalakka, Kunnukara 683594, India.

CORRESPONDING AUTHOR:

Vijay Kumar S.S., Assistant Profesor, Department of Emergency Medicine, Kanachur Institute of Medical Sciences, Deralakatte, Mangalore 575018, India

E-mail: vijay8792069357@gmail.com

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INTRODUCTION

Sodium-glucose cotransporter 2 (SGLT2) inhibitors, including canagliflozin, empagliflozin, and dapagliflozin, represent a groundbreaking class of antidiabetic medications that have revolutionized the management of type 2 diabetes.[1] These agents not only provide effective glycemic control but also offer additional benefits such as weight loss, blood pressure reduction, and significant cardio-renal protection.[2] These multifaceted advantages have positioned SGLT2 inhibitors as a cornerstone in the treatment of diabetes. However, their use is not without risks, as evidenced by the rare but potentially life-threatening complication of euglycemic diabetic ketoacidosis (eDKA).[3]

eDKA is a unique form of diabetic ketoacidosis characterized by the presence of metabolic acidosis and elevated serum ketones despite normal or near-normal blood glucose levels (<200 mg/dL).[4] Since its first description in 1973 by Munro, eDKA was considered a rare phenomenon, but its prevalence has increased in parallel with the rising prescription rates of SGLT2 inhibitors.[5] This condition poses a significant diagnostic challenge, as the absence of marked hyperglycemia may lead to a false sense of clinical stability and delays in the initiation of critical interventions.[6]

The pathophysiology of eDKA involves enhanced lipolysis and ketogenesis due to carbohydrate deficit and insulinopenia, which may be precipitated by various stressors such as fasting, infection, pancreatitis, or recent surgery.[5] Prolonged fasting, as seen during Ramadan, or specific conditions like alcohol use and gastroparesis, may further exacerbate this risk. Awareness of this complication is crucial for emergency physicians, as delayed recognition in resource-limited or high-acuity settings can have catastrophic consequences.[4] This report underscores the importance of maintaining a high index of suspicion for eDKA in patients on SGLT2 inhibitors presenting with nonspecific symptoms and metabolic acidosis, even in the absence of hyperglycemia.

CASE REPORT

A 45-year-old male a lawyer presented to the emergency department (ED) with complaints of generalized weakness, persistent nausea, and vomiting for two days. He reported reduced oral intake and adherence to strict fasting during the festival, where he consumed only fruits, fluids, and a single carbohydrate-heavy meal at night. The patient had a history of type 2 diabetes mellitus for eight years, managed with metformin (1000 mg twice daily) and dapagliflozin (10 mg daily), initiated six months ago. He denied alcohol use, smoking, recent infections, or any significant medical history. On initial evaluation, the patient was alert but appeared dehydrated and fatigued. Temperature: 98.6°F, heart rate: 110 beats/min (tachycardia), blood pressure: 104/68 mmHg, respiratory rate: 24 breaths/min (with Kussmaul's breathing) and oxygen saturation: 98% on room air.

Physical examination revealed dry oral mucosa and mild epigastric tenderness. There were no signs of focal neurological deficits, peripheral edema, or jugular venous distension. Initial laboratory workup is summarized in Table 1. Electrocardiogram (ECG) showed sinus tachycardia without ischemic changes. A chest X-ray revealed no acute findings. The clinical presentation and lab findings were consistent with euglycemic diabetic ketoacidosis (eDKA), a known but rare complication of SGLT2 inhibitors. The precipitating factors were prolonged fasting and reduced caloric intake during festival.

Table 1: Metabolic Panel of eDKA on SGLT-2

Labs	Reference Range	ED	Day 1	Day 3
Random Blood Glucose	70.2–109.8 mg/dL	176.4	111.6	100.8
Electrolytes				
Sodium	136–145 mmol/L	142	140	137
Potassium	3.4–5.1 mmol/L	4.5	3.9	3.8
Chloride	98–107 mmol/L	108	110	106
Venous Blood Gas				
pH	7.35–7.45	7.08	7.24	7.35
PaCO2	35–45 mmHg	22.5	28.4	39.1
HCO3	22–28 mmol/L	9	15	22
Anion Gap	8–16 mEq/L	28	16	10
Serum Lactate	0.5–2.2 mmol/L	1.2	0.8	0.6
Beta-hydroxybutyrate	0.2–2.8 mmol/L	7.5	2.1	0.8

eDKA: Euglycemic diabetic ketoacidosis; SGLT-2: Sodium-glucose cotransporter 2; PaCO2: Partial pressure of carbon dioxide; HCO3: Bicarbonate.

The patient was promptly initiated on aggressive management upon presentation to the ED. Intravenous fluid resuscitation was prioritized, with a bolus of 1 liter of normal saline administered immediately, followed by a continuous infusion to restore intravascular volume and hydration. As the serum glucose level decreased below 250 mg/dL, the fluids were transitioned to 5% dextrose in half-normal saline to prevent hypoglycemia. Concurrently, a continuous intravenous regular insulin infusion was started at a rate of 0.1 units/kg/hour, with blood glucose and electrolyte levels monitored hourly. Electrolyte management was carefully undertaken, with close monitoring of serum potassium levels. Although the initial potassium level was within normal range, potassium was proactively added to subsequent infusions to mitigate the risk of hypokalemia induced by insulin therapy. To address the severe metabolic acidosis (pH 7.08 and bicarbonate 9 mmol/L), a sodium bicarbonate infusion was initiated. The patient was shifted to critical care.

In critical care, the patient's euglycemic diabetic ketoacidosis (eDKA) was managed with intravenous insulin infusion, adjusted according to frequent blood glucose measurements. Serum electrolytes, blood gases, and anion gap were monitored every four hours, and intravenous fluids ensured adequate hydration. After 24 hours, metabolic parameters improved significantly, and within 48 hours, acidosis resolved. Insulin therapy transitioned to subcutaneous insulin glargine and aspart. After four days, the patient was stable and discharged. Dapagliflozin was discontinued, and the patient was educated on lifestyle changes to avoid prolonged fasting or drastic diets. Follow-up appointments and nutrition counseling were arranged to optimize diabetes management and prevent future eDKA episodes.

DISCUSSION

(SGLT2 inhibitors have emerged as an important class of medications in the management of type 2 diabetes mellitus due to their proven cardiovascular and renal benefits.[7] Studies have consistently shown their ability to reduce the risk of myocardial infarction, stroke, and chronic kidney disease progression while offering the advantage of a low risk of hypoglycemia.[3] However, their use is not without risks, particularly the development of eDKA, an infrequent but serious complication. This case underscores the importance of recognizing eDKA, especially in the ED, where timely intervention can significantly impact outcomes.[8]

Unlike classic diabetic ketoacidosis (DKA), eDKA is characterized by metabolic acidosis with an elevated anion gap and significant ketosis but without marked hyperglycemia (blood glucose <250 mg/dL).[9] This can delay diagnosis, as the absence of hyperglycemia often diverts clinicians from suspecting ketoacidosis. Early identification of eDKA requires a high index of suspicion, particularly in patients taking SGLT2 inhibitors who present with nonspecific symptoms such as nausea, vomiting, abdominal pain, dyspnea, or lethargy. Serum ketone measurement, particularly β-hydroxybutyrate, is crucial, as urine ketone tests may underestimate ketosis severity.[10]

SGLT2 inhibitors induce eDKA through a combination of mechanisms. They reduce renal glucose reabsorption, leading to glucosuria and decreased plasma glucose levels, which in turn suppress insulin secretion and enhance glucagon release.[11] The resultant low insulin-to-glucagon ratio promotes lipolysis and hepatic ketogenesis. Additionally, SGLT2 inhibitors may reduce renal clearance of ketone bodies, further contributing to ketosis.[12] Physiologic stressors such as acute illness, surgery, fasting, or dehydration exacerbate these effects by increasing counter-regulatory hormones, such as cortisol and catecholamines, which further drive lipolysis and ketogenesis.[13]

Our patient's case highlights the synergistic role of prolonged fasting in precipitating eDKA. Fasting induces a carbohydrate-deficient state, which promotes lipolysis and ketogenesis.[14] In diabetic patients, especially those on SGLT2 inhibitors, this metabolic shift can rapidly progress to ketoacidosis.[15] Any physiologic stressors exacerbated the condition by further elevating glucagon levels and reducing insulin activity. This case aligns with reports indicating that decreased oral intake is the most commonly cited precipitant of eDKA in patients taking SGLT2 inhibitors.[16]

The management of eDKA parallels that of classic DKA, with some nuances. Fluid resuscitation is critical to restore intravascular volume and improve tissue perfusion.

Intravenous insulin therapy should be initiated alongside dextrose-containing fluids to prevent hypoglycemia, given the relative euglycemia in eDKA.[17] Close monitoring of serum electrolytes, particularly potassium, is essential, as insulin therapy drives potassium intracellularly, risking hypokalemia. Discontinuation of SGLT2 inhibitors is mandatory in the acute setting.[18]

Preventative strategies for eDKA are paramount. Patients on SGLT2 inhibitors should be educated about the risk of ketoacidosis, particularly in scenarios involving reduced oral intake, dehydration, or acute illness.[19] Temporary discontinuation of SGLT2 inhibitors during fasting periods, perioperative settings, or intercurrent illness is recommended to mitigate the risk. Clinical guidelines suggest withholding SGLT2 inhibitors at least 3 days before elective procedures or other stressful situations. However, the pharmacodynamic effects of these medications may persist for up to 9–10 days, necessitating extended vigilance.[20]

This case emphasizes the need for emergency physicians to maintain a high index of suspicion for eDKA in diabetic patients presenting with unexplained acidosis, even in the absence of significant hyperglycemia. With the increasing prevalence of SGLT2 inhibitor use due to their cardiorenal benefits, eDKA recognition and management are becoming essential skills in emergency medicine. Appropriate patient counseling, proactive risk mitigation strategies, and prompt ED interventions can prevent adverse outcomes and improve the safety profile of these valuable medications.

CONCLUSION

This case underscores the importance of recognizing eDKA as a rare but significant complication of SGLT2 inhibitors, particularly in the context of physiologic stressors such as fasting or acute illness. Emergency physicians must maintain a high index of suspicion for eDKA in diabetic patients presenting with non-specific symptoms and metabolic acidosis, even with normal glucose levels. Prompt diagnosis and treatment, including cessation of SGLT2 inhibitors, insulin therapy, and fluid resuscitation, are crucial. This case highlights the need for patient education on the risks of fasting and SGLT2 inhibitor use to mitigate preventable complications.

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