A Case of SGLT-2i Induced Euglycemic Diabetic Ketoacidosis in the Setting of Gastrointestinal Stress

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ABSTRACT
Euglycemic DKA (euDKA) is a rare, uncommon variant of DKA, characterized by the imbalance between insulin and counterregulatory hormones. Lately, the use of SGLT2 inhibitors is known to incite euDKA, which is often missed on initial presentation. In this case, we present a scenario of a 61-year-old African American male with a history of hypertension, CAD s/p CABG, and type 2 diabetes mellitus on SGLT2 inhibitors (empagliflozin) with a clinical picture of normoglycemic DKA process. With a pH of 7.14, bicarbonate of 8 mEq/L, anion gap (AG) of 17mEq/L, ketoacidosis, and glucosuria, the patient met criteria for euDKA; however, the initial clinical diagnosis of euDKA was overlooked by the possibility of an underlying infectious gastroenteritis, given his recent history of travel with passengers with similar presentation, causing a delay in euDKA management. The management of euDKA is like that of a typical DKA, inciting aggressive fluid resuscitation and insulin, followed by a permanent discontinuation of SGLT2. Thus, this case highlights the importance of understanding SGLT2 induced euDKA and its early diagnostic and timely management to prevent further complications.

Introduction
Diabetic ketoacidosis (DKA) is a metabolic disorder triggered by various precipitants, leading to frequent hospitalization. The metabolic derangements associated with DKA include hyperglycemia, ketonemia, acidosis, induced by prolonged states of starvation, medication nonadherence, etc. Euglycemic DKA (euDKA) is a rare, uncommon variant of DKA, characterized by the imbalance between insulin and counterregulatory hormones, with an elevated glucagon/insulin ratio. It can potentiate significant complications, such as dehydration, if not recognized and managed early with fluids, dextrose, and insulin. A rise of euglycemic DKA, with 2.6-3.2% of DKA admissions, have been found to be attributed to the increased use of sodium-glucose cotransporter inhibitors (SGLT2i) [1,2].

Learning Points
1. Identify etiologies of euglycemic DKA (euDKA)
2. Learn to recognize signs and symptoms of euglycemic DKA (euDKA)
3. Differentiate between symptons of GI disturbances vs euglycemic DKA (euDKA)
4. Consider euglycemic DKA on initial presentation even if with a normal serum glucose
5. Understand the importance of rare adverse effects of SGLT2i

Case Presentation
A 61-year-old African American male with a past medical history of hypertension, CAD s/p CABG, type 2 diabetes mellitus, presented to the ER after flight travel, with a 1week history of fever, diffuse abdominal pain, nausea, diarrhea, and persistent vomiting followed by a near-syncopal episode. His home diabetic regimen is empagliflozin 25 mg QD and sitagliptin-metformin 50-1000 mg BID.

Diagnostic Assessment/Treatment
On admission, his vital signs were temperature of 36.4 deg C, BP of 134/59 mmHg, HR of 84, RR of 19 breaths/min, SpO2 92%. Physical exam was significant for dry mucous membranes and generalized abdominal tenderness. Laboratory findings on admission, revealed an acidemia with a pH of 7.144, bicarbonate level of 8 mEq/L, AG of 17 mEq/L, with blood glucose 173 mg/dl, 3+ glucosuria, 3+ ketonuria, trace leukocyte esterase, and proteinuria, with a normal lactate, thus meeting the criteria for euglycemic DKA. His recent HbA1c was 9.3. CT abdomen and pelvis was performed, showing no evidence of colitis/ acute mesenteric ischemia. Significant factors included his recent history of prolonged travel, and passengers with similar symptoms.
of gastroenteritis. He was started on IV bicarbonate infusion given his acidic state and initial clinical presentation of gastroenteritis, causing a delay in treatment of his euglycemic DKA. Upon initiation of bicarbonate, his AG significantly worsened on day 2, prompting us to consider a differential diagnosis, including euglycemic DKA as the principal cause of his underlying acidosis. During his hospitalization, given the previously reported episodes of ketoacidosis with poor glycemic reserve at baseline, the bicarbonate drip was discontinued, in light of worsening AG. He was then initiated on aggressive IV fluids with D5NS and IV insulin infusion at 0.1 U/kg/hr, which corrected the AG and ketosis, resulting in significant clinical improvement. On day 4 of admission, he was counseled on proper diabetic education and medical management, and advised to discontinue his use of empagliflozin, and was discharged on an insulin regimen and glipizide, and to resume his home medication—sulfonylurea-metformin BID—to achieve optimal glycemic control.

Discussion

SGLT2i are newer diabetic medications that have been associated with potential benefits, such as renoprotective and cardioprotective effects, in diabetics often outweighing the risks, such as genitourinary infections and the very rare euglycemic DKA. Recently, there is mounting evidence of euglycemic DKA precipitated by SGLT2i, which presents as a diagnostic obstacle to many physicians, due to its atypical presentation. In this case, various stressors, such as a prolonged fasting state, possible gastrointestinal infection due to recent travel, etc., may have triggered DKA. Other precipitants of DKA include anorexia, gastroparesis, ketogenic diet, pregnancy, excessive alcohol consumption, sepsis/infections, pancreatitis, cirrhosis, cardiovascular events, and recent major surgeries [1,2]. The criteria for euglycemic DKA is defined as the presence of metabolic acidosis (pH <7.3, and serum bicarbonate <18 mEq/L), ketosis, and a blood glucose <200 mg/dL, all of which were met. In euDKA, insulin deficiency and resistance are milder compared to standard DKA, hence, glucose overproduction and underutilization are less [5]. By inhibiting reabsorption of glucose in the proximal tubule, SGLT2i can reduce both fasting and postprandial blood glucose, while also lowering body weight and blood pressure [2,3]. Various SGLT2i, such as empagliflozin, canagliflozin, and dapagliflozin, have shown great efficacy in recent years in controlling diabetes with added protective effects. Although the half-life is 1 to 13 hours, their systemic effects can be prolonged several days after discontinuation, and it should be advised to discontinue at least 3 days prior to anticipating stressors, such as surgery. Overall, treatment of euDKA inculcates aggressive fluid resuscitation with isotonic saline or lactated ringer’s solution at the rate of 1 to 1.5 L/hr isotonic fluids during the initial 1 to 2 hours, after which continuous insulin infusion is initiated with concomitant K+ level monitoring, at a rate of 0.05 to 0.1 U/kg/hr. In euDKA, as serum glucose is typically <250 mg/dL, D5 should initially be added to fluids to avoid risk of hypoglycemia and expedite ketosis clearance [9]. If persistent ketoacidosis noted, increment in D5 to D10 is advised to discontinue at least 3 days prior to anticipating stressors, such as respiratory failure, cerebral edema, myocardial infarction, seizures, coma, and ultimately death [5,13].

Conclusion

Delineation of euglycemic DKA presents as a diagnostic challenge for clinicians in the initial stages resulting in treatment delay and gaps in patient care. Given the presence of normoglycemia, many clinicians omit DKA as the primary diagnosis, as presented in this case. In March 2015, the US Food and Drug Administration (FDA) issued a warning for SGLT2 inhibitors-associated diabetic ketoacidosis, after 20 cases had been reported subsequently followed by 73 cases of diabetic ketoacidosis requiring hospitalization or ER visit [7]. It is crucial for physicians to maintain a high index of suspicion in diagnosing euglycemic DKA by understanding its underlying pathophysiology and the impending adverse, but rare effects of SGLT2i in both type 1 and type 2 diabetes mellitus.

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Contributors

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Data Availability Statement

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References


