CLINICAL VIGNETTE

Euglycemic Diabetic Ketoacidosis from Empagliflozin and Gallstone Pancreatitis

Robert Li, MD, PhD and Harpreet Sidhu, MD

Clinical Presentation

A 26-year-old woman with non-insulin dependent diabetes on metformin, semaglutide, and empagliflozin is transferred from an outside hospital with 2 days of sharp right sided abdominal pain and nausea. Labs at the outside hospital were notable for elevated lipase of 800 U/L, with normal glucose, liver chemistries, and leukocytosis of 12.1. Abdominal ultrasound showed cholelithiasis but no bile duct dilatation. Due to insurance reasons, the patient was transferred for further management. Labs on transfer showed improvement of lipase to 107 U/L, normal liver enzymes, white blood cell count of 8.6, and glucose of 106 mg/dl. She remained afebrile and normotensive and reported improvement in her abdominal pain.

Several hours after admission, a consultant noted her serum bicarbonate was undetectable with an incalculable anion gap. Stat arterial blood gas showed acidemia with a pH of 7.21, pCO_2 of 19 mmHg, and HCO_3 of 7.6 mmHg. Beta hydroxybutyrate was elevated at 5.90 mmHg. Glucose was 126 mg/dl. IV insulin and D5W were started for diabetic ketoacidosis. Over the next 36 hours, her anion gap metabolic acidosis resolved along with her pancreatitis. The cause of her euglycemic diabetic ketoacidosis was attributed to a combination of pancreatitis and use of empagliflozin. She was converted to subcutaneous insulin therapy and empagliflozin was discontinued.

Discussion

Diabetic ketoacidosis (DKA) is life-threatening acute complication of diabetes mellitus. It primarily occurs in type 1 diabetes but can also occur in type 2 diabetes with acute illness such as trauma, infection, or acute coronary syndrome.[1,2] DKA is characterized by a triad of metabolic anion gap acidosis (arterial pH <7.3, serum bicarbonate < 18 mEq/L), ketosis, and hyperglycemia (glucose > 250 mg/dl).[3]

In contrast, euglycemic diabetic ketoacidosis is characterized by metabolic anion gap acidosis and ketosis with a serum glucose < 250 mg/dl.[3] The absence of hyperglycemia results in the absence of polyuria and polydipsia with presenting symptoms often consisting of tachypnea, anorexia, and malaise.[4] Due to the lack of overt hyperglycemia, early testing for metabolic acidosis and ketosis is required to identify these patients.[4] Euglycemic diabetic ketoacidosis is a relatively rare presentation, reported in 2.6 – 3.2% of DKA cases.[5,6] Etiologies associated with development of euglycemic DKA include use of certain medications including a common class of diabetes medications, sodium/glucose cotransporter-2 inhibitors, pregnancy, decreased caloric intake, heavy alcohol use, insulin use, pancreatitis, chronic liver disease/cirrhosis, and cocaine abuse.[5] With the popularization of sodium/glucose cotransporter-2 inhibitors (SGLT-2 inhibitors) as a treatment for diabetes, heart failure, and chronic kidney disease, the incidence of euglycemic DKA has been rising.[7]

SGLT-2 inhibitors block the SGLT-2 cotransporter in the early proximal renal tubule which results in glucosuria and lowering of plasma glucose concentrations.[8] In susceptible individuals, glucosuria can result in a state of carbohydrate deficit and hypovolemia which results in increased glucagon production and ketogenesis while maintaining euglycemia.[9,10] Moreover, SGLT-2 inhibitors can also directly stimulate glucagon release from pancreatic alpha cells and inhibit ketone body excretion by the kidneys.[9,10]

Risk factors for development of euglycemic DKA while taking SGLT-2 inhibitors include: (1) reduction or omission of insulin doses including insulin pump malfunction (2) low carbohydrate intake (3) excessive alcohol intake (4) nausea and vomiting including from use of glucagon-like peptide 1 agonists (5) infection or fever (6) myocardial infarction (7) heart failure (8) trauma and (9) surgery.[7,11]

Diagnosis of euglycemic DKA is one of exclusion.[12] Other causes of anion gap metabolic acidosis including alcohol intoxication, sepsis, lactic acidosis, drug overdoses, starvation ketosis, and chronic liver disease must be excluded.[3] An unexplained anion gap metabolic acidosis in a diabetic patient should prompt an evaluation of risk factors including pregnancy, surgery, fasting, infection, and SGLT-2 inhibitor use.[3] Recommended laboratory testing includes serum and urine ketones, glucose, electrolytes, renal function, blood gas analysis, lactic acid, chest x-ray, and EKG.[3]

Treatment of euglycemic DKA is similar to DKA and starts with IV insulin, fluid resuscitation, and correction of electrolyte abnormalities.[3] Due to the non-elevated initial glucose, early use of dextrose (5% or 10%) infusion will be required to prevent hypoglycemia and allow the IV insulin to suppress ketogene-

sis.[12] DKA is resolved when pH > 7.3, serum bicarbonate > 15 mmol/L, and blood ketone level < 0.6 mmol/L.[1]

Euglycemic DKA is a rare but life-threatening condition that is increasing with the popularity of SGLT-2 inhibitor drugs. A high index of suspicion and early diagnosis and treatment can prevent potentially fatal outcomes.

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