

## “It just didn’t hit the sweet spot!”: case report SGLT-2 inhibitor-induced euglycemic diabetic ketoacidosis(DKA)

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### Introduction:

SGLT2 inhibitors were hailed as revolutionary drugs when first approved for the treatment of diabetes in an era of unprecedented cases. Introduced in 2013, the further trials of empagliflozin removed excess glucose in 2015, and the study of dapagliflozin in chronic kidney disease in 2020 accelerated their use due to demonstrated cardiovascular and renal benefits, resulting in a nearly 114.6% increase between 2016 and 2021. Reports started emerging soon in 2015 of a SGLT-2 inhibitor-related cause of euglycemic diabetic ketoacidosis (EDKA). Although the incidence of diabetic ketoacidosis (DKA) due to SGLT-2 inhibitors is estimated to be 0.1%, they can increase the risk of DKA in T2DM by 7-fold. Of note, euglycemia was not always reported. The diagnosis of DKA is established via a triad of hyperglycemia above 250mg/dl, ketonemia, and metabolic acidosis with elevated anion gap. EDKA, however, lacks the classic hyperglycemia element and thus can delay clinical suspicion. Life-threatening if not suspected early, EDKA has to be managed appropriately with fluids, dextrose, and insulin. Owing to the increased prevalence of SGLT2 inhibitors, the role of multidisciplinary teamwork and high suspicion can help evaluate patients with such presentations.

### Case Report:

A 40-year-old woman, with a known case of recurrent pancreatitis with pancreatic divisum and stricture of pancreatic duct, presented to the ED with worsening abdominal pain, nausea, and vomiting of 1 week duration. Clinically, she appeared alert and well-oriented. Her laboratory investigations revealed an elevated lipase level consistent with recurrent pancreatitis. However, reported CO<sub>2</sub> of <5, leukocytosis, and anion gap acidosis with pH levels of 7.2 were alarming. Mandating the administration of bicarbonate to counter her acidosis, further review of CT imaging and lactate acid levels did not reveal possible causes such as necrotizing or infectious pancreatitis. The patient was aggressively hydrated and empiric antibiotics were withheld. A concern was raised about the possibility of DKA, specifically euglycemic DKA for this patient whose medication review showed empagliflozin. To this end, a beta-hydroxybutyrate level and urine analysis were ordered. Results showed elevated ketonemia and ketonuria and correlated with mildly elevated glucose of 160. The patient was admitted with acute pancreatitis with DKA to ICU for further management and was duly discharged after resolution within a week with no further complications.

### Discussion:

These agents’ mechanism of urine glucose loss creates a state of carbohydrate deficiency and volume depletion, thereby increasing the glucagon/insulin ratio and resulting in severe dehydration and ketosis. Moreover, recent studies find that SGLT2 inhibitors also stimulate glucagon release from pancreas and decrease the removal of ketone bodies by the kidneys, thus causing further metabolic acidosis. The laboratory picture of euglycemia is mainly due to urine glucose loss and SGLT2 inhibitor-triggered hypoinsulinemia. This creates the constellation of laboratory findings in euglycemic diabetic ketoacidosis induced by these drugs. Ketosis can be triggered through pregnancy, alcohol, surgery, infection, or starvation in patients taking these medications. According to the American Diabetes Association, 1 to 1.5 l/hour isotonic fluids are recommended during the first 1 to 2 hours. In contrast to DKA management, since serum glucose in EDKA is less than 250 mg/dl, dextrose 5% should initially be added to the fluids to avoid hypoglycemia and hasten clearance of ketosis, followed by continuous insulin, starting at a rate of 0.05 to 0.1 U/kg/hour. Consider increasing the amount of dextrose to 10% if ketoacidosis persists on D5%.

### Conclusion:

EDKA is a challenging diagnostic dilemma that is critical to be aware of with the growth of widespread usage of SGLT2 inhibitors. The absence of hyperglycemia is a conundrum for physicians in the emergency department and intensive care.

### Keywords:

Euglycemic diabetic ketoacidosis (EDKA), SGLT2 inhibitor-induced EDKA, diabetic ketoacidosis.