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## CLINICAL VIGNETTE

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# A Case of Euglycemic Diabetic Ketoacidosis in a Patient Treated with Empagliflozin

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### Abstract

One of the most dangerous complications of Diabetes mellitus is diabetic ketoacidosis, the accumulation of ketoacids in the body. A lesser known form that has become more prevalent in the diabetic population is euglycemic diabetic ketoacidosis (euDKA). This phenomenon presents with elevated anion gap metabolic acidosis and ketonuria, but a normal or mildly elevated blood glucose level. Unfortunately, the latter characteristic makes euDKA especially difficult to detect. In the recent years since their release, use of SGLT2 inhibitors has increased in Type 2 diabetics.<sup>1</sup> In this report we present a diabetic patient on outpatient empagliflozin who initially presented with choledocholithiasis and was later found to have euDKA. This case will review the pathophysiology of euDKA and its association with SGLT2 inhibitor agents.

### Introduction

Diabetic ketoacidosis (DKA) is traditionally defined by hyperglycemia, metabolic acidosis, and ketosis in blood serum and urine. However, some diabetic patients have been known to present with a form of DKA with blood glucose below 250mg/dL.<sup>2</sup> This condition is now known as euglycemic diabetic ketoacidosis (euDKA). Patients have the majority of the core findings of DKA without hyperglycemia are deemed to have euglycemic DKA. Blood glucose levels in DKA are typically above 300 mg/dL. EuDKA is defined as a triad comprising high anion gap metabolic acidosis with positive serum and urine ketones when serum glycemic levels are <250 mg/dL.<sup>2</sup>

### Case

A 71-year-old woman with well controlled Type 2 Diabetes mellitus presented with recurrent abdominal pain and nausea. MRCP revealed a 2.1cm gallstone in the CBD, and she was admitted for stone removal via ERCP. The patient reported a 15 pound weight loss within the last 3 months due to poor PO intake from nausea. She also developed new dizziness, chills, sweating, and subjective fevers a few days prior to admission.

On physical examination, the patient was a very thin woman of East Asian descent with mild temporal muscle wasting – consistent with her story of recent anorexia and weight loss. She otherwise appeared healthy, without neuropathy, retinopathy, or foot ulcers. She did have some generalized abdominal ten-

derness and nausea, but manageable with NSAIDs and anti-emetics only.

Her diabetes was very well controlled, with A1C at 7.6%. She had been compliant with her outpatient medications, which included metformin and empagliflozin. She had never required prior insulin therapy. Her blood glucose on arrival was 88. On admission she had an anion gap metabolic acidosis of 17 with decreased bicarbonate level of 19, but attributed this to starvation ketosis in the setting of her anorexia and weight loss.

She remained NPO and was given intravenous lactated ringers. The ERCP went well, and she was subsequently placed back on a regular diet. However the patient showed recurrent hypokalemia and hypophosphatemia upon initiation of feeding. It was at this point that we re-examined admission labs for alternative diagnoses and discovered her initial beta-hydroxybutyrate level elevated to 25.3mg/dL. Her labs eventually normalized with PO intake and electrolyte repletion, and the patient was discharged in stable condition.

### Discussion

Euglycemic DKA has been traditionally associated with Type 1 Diabetes due to a lack of insulin, which normally releases glucose in the bloodstream during times of stress. This sets off counterregulatory hormones, such as glucagon, catecholamines, and cortisol, which increase lipolysis and proteolysis. As a result, ketones form and accumulate.<sup>1</sup> It can still manifest in the Type 2 disease form, but less frequently and only in cases where the majority of pancreatic beta cells have already burned out.<sup>3</sup> However, in recent years, there has been a rising prevalence of euDKA among Type 2 diabetics due to increased use of SGLT2 inhibitors. SGLT2 inhibitors lower blood sugar levels by rapidly increasing glucose excretion in the urine which can last over 24 hours, effectively inducing a similar glucose-deficient environment. Canagliflozin, the first of its kind to be released on the mass market in 2013, has been the most often associated with euDKA, although it is unclear whether this is due to the drug specifically or whether it has simply been around longer than its counterparts.<sup>4</sup>

EuDKA can be difficult to diagnose, as often patients taking SGLT2 inhibitors that are most often affected report a history of well controlled blood sugars readings. It is the absence of elevated glucose in the bloodstream that puts them at higher risk

of ketoacidosis. Studies have shown that euDKA manifests most commonly in times of stress such as concurrent illness, alcohol use, and/or post-surgery<sup>1,5</sup> – conditions we often encounter in the hospital. Furthermore, to complicate matters, these individuals do not always present with the same complaints as classic DKA. Because they lack hyperglycemia, they may not have overt dehydration initially, and many of them have been noted to have only ambiguous symptoms such as nausea, malaise, or decreased appetite.<sup>2,6</sup>

Our patient presented with anorexia, nausea, and abdominal pain, but we attributed them to her diagnosis of cholelithiasis. It is possible that the new dizziness, malaise, and subjective fevers she complained of in the few days prior to admission were due to the new development of euDKA. She also had a metabolic acidosis on initial labs which we attributed to starvation ketosis, but this would not explain the elevated beta-hydroxybutyrate we later found in her blood. Furthermore, our patient was a thin East Asian female. One study reported that East Asians with Diabetes tended to be leaner, with their condition more often linked to beta-cell insufficiency. Thus, they are at an increased risk of euDKA with SGLT2 inhibitor use.<sup>3</sup>

As with classic DKA, the treatment of euDKA is IV hydration with concurrent IV insulin until the anion gap is closed. Great care must be taken to monitor electrolytes, as there is significant shifting of potassium and phosphate into the cells. Our patient also showed recurrent drops of both electrolytes with frequent repletion. Initially, we attributed this to refeeding syndrome after prolonged anorexia, but it is more likely that her euDKA also contributed. We did not start IV insulin due to delayed detection, but fortunately, her case was mild, and she managed to recover on PO food intake and IV fluids alone. A more severe form of the disease may have progressed to worse complications before a proper diagnosis was made.

## Conclusion

SGLT2 inhibitors are common agents for effective management of Diabetes mellitus. They have shown significant improvement in blood sugar control in the past 5 years since market release. However, they have been associated with euglycemic DKA, a severe adverse reaction that can manifest with only subtle warning signs. Clinicians should be aware of euDKA and have low threshold to check ketone levels when treating diabetic patients prescribed these agents.

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