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CLINICAL VIGNETTE

Euglycemic Diabetic Ketoacidosis in Conjunction with a Sodium Glucose Cotransporter-2 (SGLT2) Inhibitor with Intermittent Fasting and Ketogenic Diet

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Case Report

A 50-year-old male with type 2 diabetes mellitus (T2DM), hypertension and hyperlipidemia presented to the emergency room (ER) with nausea, vomiting and abdominal pain. He developed nausea and non-bloody emesis the day prior to presentation. He attributed his symptoms to food poisoning and recalled eating mayonnaise from a non-refrigerated open container that had been sitting out for an unknown amount of time. He tried carbonated beverages which helped previously with no relief. Nausea and emesis presented with small streaks of bright red blood. After several episodes of emesis, he noted onset of abdominal pain in the epigastric region initially, described 5/10 severity ache which increased to a 10 out of 10 in severity. He reported passing a single black stool the day prior to ER presentation. He had taken non-steroidal anti-inflammatories (NSAIDS) for a few days for back pain. Two months prior he started Synjardy, a sodium glucose cotransporter-2 inhibitor (SGLT2) combined with metformin.

Upon arrival to the ER his vital signs included a temperature of 37.6°C, tachycardia at 130 bpm, respiratory rate of 17/min, blood pressure of 175/91 and room air oxygen saturation of 92%. Physical exam was notable for dry mucous membranes and a soft but tender abdomen in the epigastric region without rebound or guarding. Labs were notable for a leukocytosis of 20, hemoglobin of 21.0, carbon dioxide less than 10, creatinine 1.41, glucose 298, positive serum ketones and a pH of 7.26. ECG showed sinus tachycardia at 120. Chest x-ray showed no acute pathology and CT of the abdomen and pelvis was unremarkable for acute intra-abdominal pathology. He was admitted to the ICU. Blood cultures were drawn and judicious fluid resuscitation with an insulin drip started for concern of diabetic ketoacidosis (DKA). He was also given intravenous pantaprazole for concern of melena.

Gastroenterology was consulted for reported melena, with elevated initial hemoglobin was elevated in the setting of dehydration. An EGD showed reflux esophagitis without bleeding and non-bleeding duodenal ulcers with no stigmata of bleeding. He was continued on pantaprazole with no melena during his hospitalization.

He was weaned off the insulin drip and transitioned to scheduled Lantus and Lispro insulin. His acute kidney injury resolved after adequate fluid resuscitation and his leukocytosis and erythrocytosis returned to normal range. Additional history revealed that in addition to recently starting empagliflozin/metformin, he also changed to intermittent fasting and ketogenic diet. Endocrinology consultants agreed his presentation was multifactorial from medication, intermittent fasting and a ketogenic diet. He made a complete recovery and was instructed to continue the insulin regimen started during admission and replace empagliflozin/metformin with metformin alone. He was further educated on the risks of an intermittent fasting and ketogenic diet.

Discussion

Managing type 2 diabetes (T2DM) has advanced with the recent use of sodium glucose cotransporter-2 (SGLT2) inhibitors and lifestyle modifications including ketogenic diet and intermittent fasting. While these interventions provide significant glycemic control, weight loss and cardiorenal protection, their potential interactions can lead to euglycemic diabetic acidosis (eDKA) which needs to be better understood. The integration of the SGLT2 inhibitors and lifestyle modifications requires careful patient selection, education and monitoring to minimize potential risks.

Euglycemic DKA is a rare, life-threatening medical emergency. It is uncommon, comprising between 2.6% to 3.2% of DKA admissions.[1] However, the incidence of eDKA has increased with increased use of SGLT2 inhibitors for T2DM.

SGLT2 inhibitor-associated ketoacidosis has been recently analyzed in response to post marketing surveillance of DKA in patients with diabetes mellitus.[2] A review and meta-analysis reported SGLT2 inhibitors were statistically associated with a small, increased risk of DKA (0.18%) versus the control (0.09%).[3] It is estimated that SGLT2 inhibitors are associated with an approximate 7-fold increased risk for developing ketoacidosis. Most of these cases (71%) were categorized as eDKA.[4]

Low-carbohydrate, ketogenic diets have recently become popular lifestyle interventions for T2DM. This diet restricts carbohydrates, promoting a ketogenic state of fatty acid metabolism. Although ketogenic diets induce a state of ketosis, they alone are not commonly associated with DKA. However, their use

with SGLT2 inhibitors has been reported to increase risk of eDKA.[5] Low-carbohydrate, high-fat meals stimulate glucagon production and fatty acid metabolism while limiting serum glucose availability. This physiologic state is likely exacerbated by concurrent glucagon upregulation and serum glucose depletion caused by SGLT-2 inhibitors which can lead to severe acidosis with ketosis.[6] Limited supply of dietary carbohydrates combined with SGLT-2 inhibitor-induced glucosuria may create a state of DKA without elevated serum glucose.[7] This association warrants further validation.

Intermittent fasting involves alternating periods of eating and fasting in various schedules. These can include time restricted feeding and alternate-day fasting. In doing so, the body switches from using glucose as an energy source to using fatty acids, typically 12 hours after discontinuing food intake.[8] As a result, ketogenesis is stimulated similar to a ketogenic diet though in a different pathway.

Given that SGLT-2 inhibitors, a ketogenic diet, and intermittent fasting can result in euglycemic ketosis, there is an increased risk of developing this derangement when these diets and medications are combined.

Conclusion

This case highlights the importance of close monitoring of both dietary and lifestyle modifications in patients with T2DM and SGLT2 inhibitors, and the importance of nutritional education avoid eDKA. A discussion with patient should occur before initiating a SGLT2 inhibitor, especially in patients considering dietary changes. Patients on SGLT2 inhibitors are advised to keep well hydrated, have balanced meals, and consider stopping these medications during prolonged fasting.

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