The Use of SGLT-2 Inhibitors Coupled With a Strict Low-Carbohydrate Diet: A Set-Up for Inducing Severe Diabetic Ketoacidosis

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Helpees Guirguis[1], Shiela Beroukhim Afrahimi[2] and Charles Pham[1]

[1]Harbor UCLA Medical Center, Torrance, CA, USA. [2]University of California Los Angeles Medical Center, Los Angeles, CA, USA.

ABSTRACT: A 58-year-old male with a history of hypertension and non-insulin dependent type 2 diabetes mellitus (DM) was brought in by ambulance and admitted to the intensive care unit for weakness, lethargy, and altered mental status and was found to be hypotensive and subsequently diagnosed with severe diabetic ketoacidosis (DKA). A thorough investigation into precipitating factors for his DKA was largely unrevealing; an extensive infectious work- up was negative and the patient's history was otherwise only significant for starting a ketogenic diet 1 month prior while simultaneously being on a sodium-glucose transport protein 2 (SGLT-2) inhibitor, namely empagliflozin. Literature investigation revealed that a strict low carbohydrate diet can rarely lead to DKA in the setting of SLGT-2 inhibitor use.

KEYWORDS: Diabetic ketoacidosis, type 2 diabetes mellitus, SGLT-2 inhibitors, ketogenic diet

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CORRESPONDING AUTHOR: Helpees Guirguis, Department of Internal Medicine, Harbor UCLA Medical Center, 1000 West Carson Street, Box 400, Torrance, CA 90509, USA. Email: helpees.guirguis@gmail.com

Background

SGLT-2 inhibitors are a relatively new class of oral anti-hyperglycemic agents used for persons with type 2 diabetes. The drug's main mechanism of action is via reduction of renal tubular glucose reabsorption; the drug's mechanism does not involve stimulating insulin release.[1] In addition, in clinical trials, SGLT-2 inhibitors have been shown to promote weight loss and reduce blood pressure, making them an often-attractive choice of drug for patients who have concomitant hypertension or obesity.[2] Furthermore, the EMPA-REG outcome study, a randomized double-blind placebo-controlled study, demonstrated a 38% relative risk reduction in death from cardiovascular causes in persons receiving empagliflozin in comparison to persons receiving placebo.[3] Addtionally, other studies have shown similar results including the CANVAS-R study, which integrated data from two trials involving a total of 10,142 participants with DM and high cardiovascular risk and found that Canagliflozin had a lower risk of cardiovascular events than those who received placebo.[4] A meta-analysis recently published in JAMA Cardiology included a total of 6 placebo-controlled clinical outcome trials in addition to EMPA-REG outcome (CANVAS, DECLARE-TIM 58, CREDENCE, VERTIS CV) of four SGLT-2 inhibitors in patients with type 2 DM and found growing evidence base that SLGT-2 inhibitors in general are associated with favorable cardiovascular and kidney outcomes.[5]

In recent years, the ketogenic diet has gained popularity as a regimen for rapid weight loss through consumption of low carbohydrate and high fat foods.[6] This type of diet causes metabolic changes including glycogen store depletion, ketogenesis and gluconeogenesis.[6] A growing population of patients with type 2 DM have adopted a ketogenic diet as a means of reaching their desired weight goal and also improving glycemic control, sometimes (or usually) without the guidance of a physician.[7] A nonrandomized study of the ketogenic diet in persons with type 2 DM showed a 1.3% reduction in glycosylated hemoglobin at 1 year in the ketogenic group.[8] Notably, a meta-analysis of randomized long-term studies comparing the ketogenic diet with low-fat diets for weight loss reported no difference in glycemic control among persons with type 2 DM.[9] Additionally, the ketogenic diet, despite evidence supporting its use, is limited by its potential risks including nephrolithiasis, constipation, halitosis, muscle cramps, headaches, diarrhea, restricted growth, bone fractures, pancreatitis, and multiple vitamin and mineral deficiencies.[10]

Case Presentation

A 58-year-old male presented to the emergency department with a 2-day history of generalized weakness and fatigue, confusion and slurred speech. He had a history of type 2 DM treated with metformin, empagliflozin, sitagliptin, and repaglinide. The patient, upon improvement of his condition, also endorsed having started a ketogenic diet 1 month ago along with intermittent fasting for weight loss and had stopped metformin and repaglinide but continued with the rest of his medications.

On admission, he was found to be hypothermic to 34.4°C (Ref. range 36-37.8 °C) and hypotensive with mean arterial pressures (MAPs) in the 40 to 50′s/mmHg (Ref. range 55-110 mmHg). He was somnolent but arousable on presentation, and unable to appropriately answer questions. Laboratory examination was notable for a potassium of

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5.2 mmol/L (Ref. range 3.6-5.1 mmol/L), glucose of 373 mg/dL (Ref. range 74-118 mg/dL), anion gap of 22 mEq/L (Ref. range 4-12 mEq/L), beta hydroxybutyrate level of 9.8 mmol/L (Ref. range 0.0-0.3 mmol/L), with profound acidemia on venous blood gas with pH 6.9 (Ref. range 7.33-7.43), pCO_2 36 mmHg (Ref. range 38-50 mmHg) and $HCO_3 < 5$ mEq/L (Ref. range 20-30 mEq/L). His hemoglobin A1C was 6.7% (Ref. range <5.6). A diagnosis of DKA was made and a DKA protocol was initiated including aggressive fluid resuscitation and intravenous insulin therapy.

Precipitating factors for his DKA were thoroughly investigated with no conclusive etiology; diagnostics including electrocardiogram, chest radiograph, and computed tomography (CT) scan of the abdomen were unremarkable. He was initially placed on empiric broad-spectrum antibiotics however, these were eventually discontinued given no infectious source was identified. The patient had a slow recovery, so imaging of the brain was later obtained but was again unrevealing for any acute processes.

The patient gradually recovered over the course of several days and was eventually transitioned to subcutaneous insulin. Given several case reports purporting the rare side effect of DKA with SGLT-2 inhibitors in the setting of a low-carbohydrate diet and fasting, along with the absence of any other clear precipitant, we believefelt that SGLT-2 inhibitor use combined with his ketogenic diet and intermittent fasting was the most likely etiology for his DKA. He was educated on the importance of avoiding a ketogenic diet and intermittent fasting while on an SGLT-2 inhibitor and to discuss any dietary changes with his primary care physician.

Discussion

Adverse side-effects of SGLT-2 inhibitors have been well documented and include genital infections, Fournier gangrene, decreased bone mineral density, and in rare cases, DKA.[11] However, DKA is much less common when used in patients with type 2 DM, with an incidence of less than 0.2%.[12] The United States Food and Drug Administration (FDA) issued a warning regarding the risk of DKA with the use of SGLT-2 inhibitors in 2015 based on identifying more than 70 reported cases of DKA in patients treated with SGLT-2 inhibitors, reporting that DKA was not immediately recognized because of the presence of low to normal blood glucose levels.[13]

SGLT-2 inhibition induces a rapid increase in urinary glucose excretion which leads to low plasma insulin levels resulting in reduced glucose utilization and enhanced lipolysis to promote free fatty acid (FFA) oxidation and production of ketone bodies.[13] Furthermore, reduced insulin production from pancreatic β-cells stimulates α-cells to increase plasma glucagon concentrations.[14] These changes result in decreased insulin-to-glucagon ratio, further stimulating lipolysis, augmenting the production of FFAs and inducing ketogenesis.[1] However, the median time to diabetic ketoacidosis after initiation of SGLT-2 inhibitor therapy was 2 weeks (ranging from 1-175) and 50% of cases were associated with precipitating events including acute illness (e.g. infection or surgery), reduced oral intake, and reduced insulin dose.[15] This can be exacerbated by low carbohydrate availability in the setting of a low-carbohydrate diet as well as intermittent fasting.

Our case demonstrates an example in which the use of SGLT-2 inhibitors with adherence to a ketogenic diet and intermittent fasting can lead to DKA with profound acidemia. Although our patient had symptoms of DKA including generalized weakness, and confusion, his glucose level was in the mid 300 range with a hemoglobin A1C of 6.7% yet had a pH of 6.9, demonstrating that a patient does not have to have severely uncontrolled diabetes to present in DKA and profound acidosis in such a setting. The unique presentation of DKA induced by SGLT-2 inhibitors makes its diagnosis challenging, especially when all other precipitating factors are ruled out. Furthermore, upon review of his other DM medications, none are associated with DKA making them as less likely the cause of his presentation. In this case, investigating the patient's history including his recent change in diet revealed a significant culprit for his presentation.

Although the ketogenic diet and intermittent fasting have become popular weight loss strategies, their long-term side effects have yet to be studied in-depth. One study showed that adhering to a low-carbohydrate, ketogenic diet can induce a mild compensated metabolic acidosis,[16] while another study showed that very low carbohydrate ketogenic diet is a safe nutritional intervention for the treatment of obesity in terms of acid-base equilibrium.[17] Regardless, more research is warranted to further elucidate the potential metabolic complications that can result from these dietary approaches. We encourage health care providers to remain cognizant about patients on SGLT-2 inhibitors who may be seeking a ketogenic diet and intermittent fasting as a means for weight loss, as it may induce a severe DKA.

Clinical Pearls

- The concomitant use of SGLT-2 inhibitors and a ketogenic diet may increase the risk of DKA in patients with type 2 DM.
- Severe DKA can be induced even in cases where diabetes is well controlled.
- Health care providers prescribing SGLT-2 inhibitors should counsel their patients about possible complications and side effects including refraining from a ketogenic diet

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Author Contributions

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ORCID iD

Helpees Guirguis https://orcid.org/0000-0002-4025-5441

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