Paradoxical Diabetic Ketoacidosis in a Type 2 Diabetes patient on Dapagliflozin: A Brief Case Report

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Abstract

A 48-year -old male patient with Type 2 diabetes mellitus(T2D) on insulin replacement therapy, glipizide and Dapagliflozin admitted for generalized weakness found him in euglycemic diabetic ketoacidosis which means normal or near normal glucose levels with high anion gap metabolic acidosis recovered on insulin drip per DKA protocol.

Paradoxical Diabetic Ketoacidosis in a Type 2 Diabetes patient on Dapagliflozin: A Brief Case Report

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Abstract:

A 48-year -old male patient with Type 2 diabetes mellitus(T2D) on insulin replacement therapy, glipizide and Dapagliflozin presented with generalized weakness with weight loss of 40 pounds in 6 months ever since he was started on dapagliflozin. He was hemodynamically stable on arrival with a finger stick glucose of 121 gm%. Physical exam was also unremarkable except for dry mucus membranes. His lab results on arrival are shown in Table 1. His serum osmolar gap was within the normal range. He was treated insulin dripper DKA protocol and gap was closed, the patient was clinically and biochemically back to baseline, and he was discharged home.

Delayed diagnosis of normoglycemic diabetic ketoacidosis (DKA) in adults with diabetes treated with multiple anti-diabetic drugs (e.g., sodium glucose cotransporter-2 [SGLT-2] inhibitors) can potentially increase morbidity and mortality. Patient education in terms of symptoms and signs, physician awareness of early recognition of ketoacidosis in the setting of paradoxically normal or near normal blood glucose levels in these patients is the primary focus of this case study. This is paradoxical DKA because theoretically patient is

not meeting one of the criterion for DKA which include triad of hyperglycemia, Ketoacidosis with widened anion gap, Ketonemia.

This is a short case report of presumed SGLT2 inhibitor euglycemic diabetic ketoacidosis. The main teaching point is recognition and early diagnosis of this issue when multiple diabetic medications are present with the absence of hyperglycemia.

Case Presentation:

The patient was a 48-year-old male with type 2 diabetes (T2D) requiring insulin glargine daily with prepprandial aspart insulin, metformin with glipizide (500 mg + 5 mg) daily, and dapagliflozin (10 mg once daily). His medical history was significant for hypothyroidism, hyperlipidemia, and vitamin D deficiency. He presented to the emergency room with complaints of generalized weakness for a few days, nausea, loss of appetite, lightheadedness, polydipsia, and polynocturia. He had also lost 40 pounds in the 6 months since he was started on dapagliflozin. He denied abdominal pain, chest pain, cough, shortness of breath, diarrhea, and urinary tract infection symptoms. He was hemodynamically stable on arrival with a finger stick glucose of 121 gm%. Physical exam was also unremarkable except for dry mucus membranes. His lab results on arrival are shown in Table 1. His serum osmolar gap was within the normal range. Cardiac, pancreatic enzyme, electrocardiogram, and imaging studies were unremarkable. He was managed initially with an insulin drip and intravenous fluids in the emergency room, which was continued upon admission to the critical care unit. After ˜15 hours, the anion gap was closed, the patient was clinically and biochemically back to baseline, and he was discharged home. He was counseled about medication compliance and regular follow-up with his primary care physician.

Discussion:

Dapagliflozin is an SGLT-2 inhibitor, a novel class of anti-hyperglycemic drugs approved by the U.S. Food & Drug Administration (FDA) in 2013. SGLT-2 is expressed in the proximal convoluted tubule of the nephron and mediates reabsorption of approximately 90% of filtered glucose. Gliflozins inhibit these transporters, thus promoting urinary glucose excretion. Officially, the FDA approved them only for T2D because of their beneficial effects on postprandial hyperglycemia, weight loss (to some extent), lack of hypoglycemic effects, and decreasing daily insulin requirements. They also lower blood pressure, which may be beneficial in hypertensive patients.

The incidence of normoglycemic diabetic ketoacidosis (DKA) in patients managed on SGLT-2 inhibitors has been rising [5], and triggers include insulin compliance issues, starvation, strenuous exercise, influenza, carbohydrate restriction, heavy alcohol abuse, and appendicitis. The FDA issued black box warning on this life-threatening complication. Peters et al [1] reported 13 episodes of normoglycemic DKA, including 9 on SGLT-2 inhibitors for off-label use in patients with type 1 diabetes. Hine et al [3] described two patients who developed normoglycemic DKA while being managed on dapagliflozin, which is similar to the present case.

The exact mechanism by which SGLT-2 inhibitors cause paradoxical DKA is not clear; however, it is possible that they induce ketone body acidosis [3] as shown in Figure 1. The increased glucagon/insulin ratio activates lipases, leading to adipose tissue lysis and the release of free fatty acids. These ultimately undergo beta oxidation in the liver, contributing to ketone body production. Phlorizin is a natural glucoside that has been used as a physiological and pharmacological tool for research purposes [4,5]. It nonselectively inhibits both SGLT-1 and SGLT-2. It blocks glucose absorption in the intestine and prevents glycosuria by inhibiting glucose and sodium reabsorption in the kidney. As a result, sodium concentration in the tubule increases, creating an electrochemical gradient that drives acetoacetate reabsorption. If dapagliflozin exerts a similar effect, it could also contribute to ketone body acidosis while maintaining normal or near normal glucose levels by glycosuria. Interestingly, SGLT-2 inhibitors can reportedly increase serum glucagon levels by acting directly on the pancreatic alpha cells to increase pre-proglucagon gene expression [5]. We routinely rely on the assessment of urine ketone body levels rather serum levels for diagnosing ketone body acidosis. As SGLT-2 inhibitors decrease urine ketone body levels, it is prudent to also measure serum levels and avoid

potential delays in diagnosing DKA [3].

The learning objective in this case study is early diagnosis and management of DKA in SGLT-2-treated patients with signs or symptoms of academia, ketonemia, or ketonuria. Educating treating physicians and patients who use SGLT-2 inhibitors about early DKA recognition and management is of paramount importance to reduce both morbidity and mortality. Suspicious signs and symptoms of acidosis include nausea, vomiting, abdominal discomfort or pain, weakness, myalgias, history of polynocturia, signs of dehydration, and ketonuria even in the setting of normoglycemia.

Table 1: Laboratory Results

CBC BMP

WBC: 9500 cells/?L Sodium: 129 mmol/L

Hb: 18.8 g/dL Potassium: 4.4 mmol/L

Hct: 56% Chloride: 97 mmol/L

Platelets:230 cells//?L Bicarbonate 12 mmol/L

Blood urea nitrogen: 18 mg/dL

Creatinine: 1.1 mg/dL

Glucose: 130 mg/dL

Anion gap: 20 mmol/dL

Beta hydroxybutyrate: 3 mmol/L

ABG: pH, 7.1; pO2, 127; pCO2, 18; FiO2, 21%

Abbreviations: ABG, arterial blood gas; BMP, basic metabolic panel; CBC, complete blood count; FiO2, fraction of inhaled gas that is O2; Hb, hemoglobin; Hct, hematocrit; pCO2, partial pressure of carbon dioxide; pO2, partial pressure of oxygen; WBC, white blood cells.

Figure:1 Putative mechanism showing how SGLT-2 inhibitors can cause normoglycemic DKA (SGLT-2:Sodium Glucose co transporter-2, FFA: Free Fatty Acids, DKA: Diabetic Ketoacidosis)

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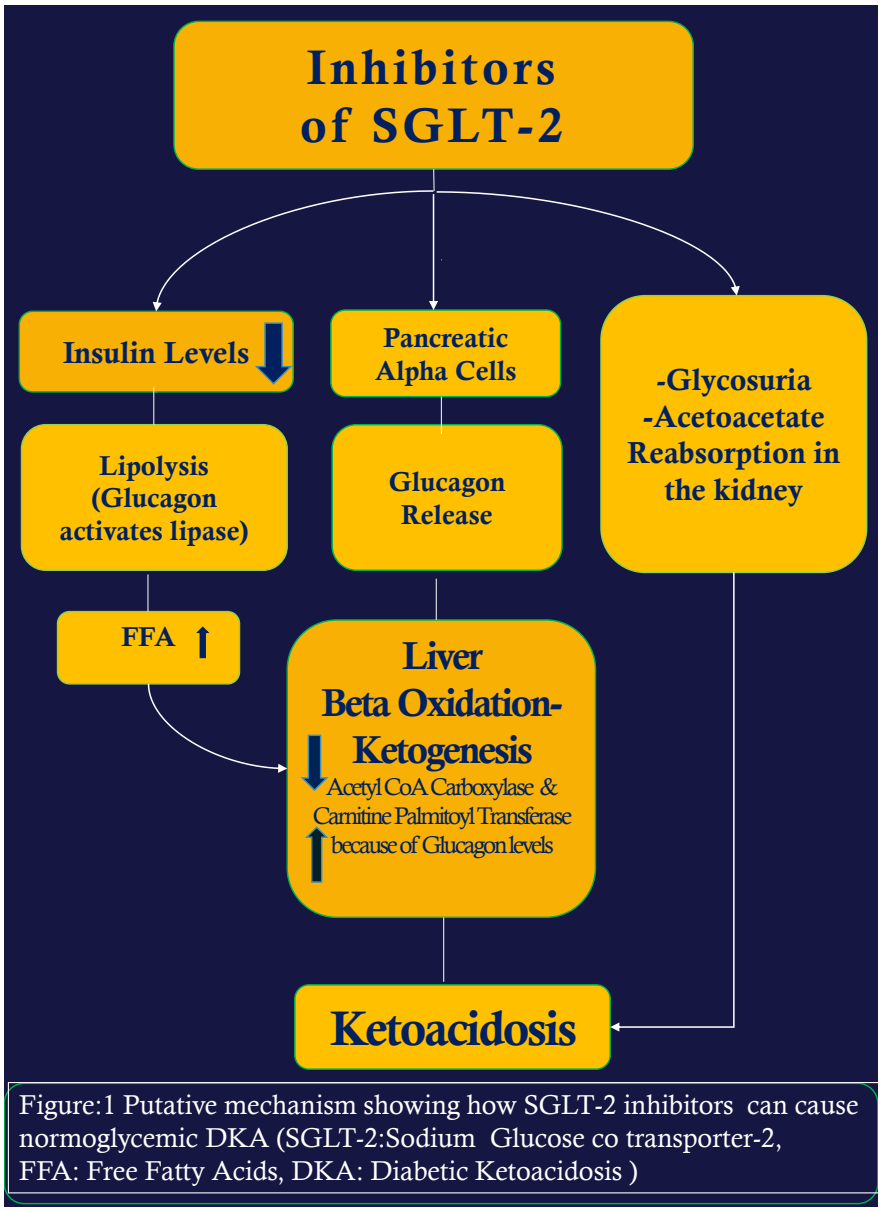

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