CASE REPORT

Normoglycemic diabetic ketoacidosis in a type 2 diabetes patient on dapagliflozin: A 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 examination was unremarkable except for dry mucus membranes. His laboratory results on arrival are shown in Table 1. His serum osmolar gap was within the normal range. He was treated insulin drip per 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 antidiabetic drugs (eg, 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 criteria for DKA which include triad of hyperglycemia, Ketoacidosis with widened anion gap, Ketonemia. This is a short case report of presumed SGLT-2 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. This is, by current definition, not DKA because theoretically, the patient does not meet one of the criteria for DKA as the patient was apparently not hyperglycemic, albeit with, ketoacidosis and widened anion gap. (ketonemia)

KEYWORDS
DKA, euglycemic DKA, anion-gap metabolic acidosis, SGLT-2 inhibitor, ketoacidosis
1 | CASE PRESENTATION

The patient was a 48-year-old man with type 2 diabetes (T2D) requiring insulin glargine daily with pre-prandial 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 polyuria. 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 examination was also unremarkable except for dry mucus membranes. His laboratory 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.

2 | DISCUSSION

Dapagliflozin is an SGLT-2 inhibitor, a novel class of anti-hyperglycemic drugs approved by the U.S. Food & Drug Administration (FDA) in 2013.1 Canagliflozin was the first SGLT-2 inhibitor was released to market and reported multiple cases on normal or near normal glucose levels with DKA similar to our patient.1 The FDA issued black box warning on this life-threatening complication. Peters et al1 reported 13 episodes of normoglycemic DKA, including 9 on SGLT-2 inhibitors for off-label use in patients with type 1 diabetes.

The incidence of dapagliflozin-associated DKA is <0.1%.2 A recent US FDA review of adverse events associated with SGLT-2 inhibitors use reported as a fatality rate of 1.54%, as compared with 0.4% for all DKA cases.3

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. This glycosuria leads to decreased sodium reabsorption in the kidney, which in turn leads to increased ketone body production.4

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.4 Studies also showed potential benefits in regard to cardiovascular mortality and morbidity such as reduction in congestive heart failure readmission rate.4

Furthermore, SGLT-2 inhibitors are also associated with an increase in plasma glucagon levels though the mechanism is unknown. It has been reported in a study5 dapagliflozin has been associated with SGLT-2 expression in pancreatic alpha islet cells resulting in an increase in plasma glucagon levels. This is possible side effect of the SGLT-2 inhibitor but fortunately good to maintain low blood glucose levels induced by fasting.5 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

The incidence of normoglycemic diabetic ketoacidosis (DKA) in patients managed on SGLT-2 inhibitors has been rising,3 and triggers include insulin compliance issues, starvation, strenuous exercise, influenza, carbohydrate restriction, heavy alcohol abuse, and appendicitis. Hine et al6 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 this atypical DKA is not clear; however, it is possible that they induce ketone body acidosis6 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

| TABLE 1 Laboratory results |
|-----------------------------|
| **CBC**                     | **BMP**               |
| WBC:9500 cells/micro L      | Sodium:129 mmol/L     |
| Hb:18.8 g/dL                | Potassium:4.4 mmol/L  |
| Hct:56%                     | Chloride:97 mmol/L    |
| Blood urea nitrogen:18 mg/dL| Bicarbonate:12 mmol/L |
| 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.
is a natural glucoside that has been used as a physiological and pharmacological tool for research purposes. 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 acetacetate 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.

Taylor et al study reported how SGLT-2 inhibitors contribute to pathogenesis of ketoacidosis directly or indirectly. Animal studies are interesting in support of SGLT-2 inhibitor inhibition of tubular reabsorption of glucose causing normoglycemia or near normoglycemia. Studies in dog demonstrated that phlorizin (a non-selective SGLT-1/ SGLT-2 inhibitor) promotes renal tubular reabsorption, which increases the electrochemical gradient driving carrier-mediated reabsorption of negatively charged ketone bodies. This combination of increased ketone body production plus decreased renal clearance would exert an additive effect to increase circulating ketone body levels. This study was done in type 1 diabetes mellitus (T1DM) patients. Thus, it is biologically possible that administration of SGLT-2 inhibitor to an insulin-dependent T1DM patient would predispose to ketoacidosis.

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.
To our knowledge, there have been no studies in literature describing the relationship between development of euglycemic DKA and dosage or duration of SGLT-2 inhibitor administration. A meta-analysis by Burke et al reported that the data on 34 patients who developed DKA due to SGLT-2 inhibitor use, of which 25(73.5%) had T2D. The average age of those presenting with DKA was 51.2 ± 16.3 years, and the average concentration of blood glucose was 265.6 ± 140.7 mg/dL (range, 68–500 mg/dL). The average values of PH and anion gap were 7.05 ± 0.15 and 21.6 ± 5.3 meq/L, respectively.9

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CONFLICT OF INTEREST
The authors have nothing to disclose.

AUTHOR CONTRIBUTIONS
Venkata Vinod Kumar Matli prepared draft and required data, literature review. Nidhi Bansal reviewed and revised manuscript for submission. Maria Fariduddin and Kwabena Asafo-Agyei helped in literature review for revision of the manuscript.

ETHICAL APPROVAL
All data generated or analyzed during this study are included in this article and its supplementary material files. Further enquiries can be directed to the corresponding author. Study received no funding from any source. Patient consent has been signed and collected in accordance with the journal’s patient consent policy.

CONSENT
Written informed consent was obtained from the patient for publication of this case report.

DATA AVAILABILITY STATEMENT
Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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