

CASE REPORT

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Euglycemic diabetic ketoacidosis induced by sodium-glucose cotransporter 2 inhibitor in the setting of prolonged fasting: a case report

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Abstract

Background: We describe a case report of a patient with type 2 diabetes on sodium-glucose cotransporter 2 inhibitor and metformin therapy fasting for Ramadan (a holy month observed in the Islamic nation) diagnosed with euglycemic diabetic ketoacidosis.

Case presentation: The patient was a 51-year-old Moroccan male with history of type 2 diabetes mellitus on dapagliflozin and metformin. He presented with abdominal pain, vomiting, loss of appetite, and shortness of breath. He observed Ramadan month by fasting an average of 14 hours daily for 30 days. The patient was admitted with severe metabolic acidosis with a high anion gap and positive ketonuria in the setting of serum glucose of 13.5 mmol/L (243 mg/dL).

The patient was rehydrated and started on insulin infusion according to the diabetic ketoacidosis protocol following the diagnosis of euglycemic diabetic ketoacidosis.

Conclusion: Dapagliflozin is associated with euglycemic diabetic ketoacidosis in the setting of prolonged fasting. Counseling and possible medication adjustment should be added to clinical practice in those planning to decrease caloric intake through dedicated fasting including Ramadan or weight-loss-directed behavioral modifications, especially if taking sodium-glucose cotransporter 2 inhibitors.

Keywords: Euglycemic diabetic ketoacidosis, EDKA, DKA, Sodium-glucose cotransporter 2 inhibitor, Dapagliflozin, Prolonged fasting, Case report

Background

Diabetic ketoacidosis (DKA) is defined by certain diagnostic criteria, including blood glucose level of more than 13.9 mmol/L (250 mg/dL), acidosis (arterial pH < 7.3 and serum bicarbonate < 15 mEq/L), and ketonemia [1]. Euglycemic diabetic ketoacidosis (EDKA) is defined as follows: blood glucose level below 13.9 mmol/L (250 mg/dL), acidosis, and development of ketonemia [2, 3].

The first case of EDKA was described by Munro in 1973, whereby he studied 211 cases of DKA, 11 of which had blood glucose levels below 16.7 mmol/L (300 mg/dL) [4]. This was classically considered a rare incident, but it is likely underreported [2]. The etiology of EDKA is unknown, but there are many stressors and conditions that can precipitate an episode in either a diabetic or healthy patient [5, 6]. Such stressors include fasting, anorexia, gastroparesis, being on a ketogenic diet, and higher alcohol consumption [3, 7]. Furthermore, conditions such as pregnancy, cirrhosis, pancreatitis, insulin pump use, sepsis, cardiovascular events, and recent major surgery also play a similar role [3, 8].

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The benefits of SGLT2 inhibitors have been extensively studied, including adequate glycemic control, weight loss, and more importantly, nephrological and cardiovascular protection [10–12]. Alternatively, life-threatening side-effects related to this class of medication, such as diabetic ketoacidosis and EDKA, have also been documented in literature [13]. Therefore, a warning is included in the drug label for SGLT2 inhibitors [9]. These medications, including canagliflozin, dapagliflozin, and empagliflozin, increase the risk of inducing EDKA [3, 15, 16]. Triggers inducing EDKA predispose the body to a carbohydrate deficit, which will result in lipid catabolism as a source of energy via the anaerobic pathway. Fatty acids are then produced by lipolysis, and high levels of fatty acids leads to ketone formation [3, 6]. Here, we present the first case of EDKA associated with 14 hours of fasting daily for 30 days while being on dapagliflozin.

The ritual of fasting in the Islamic nation is most significant in Ramadan. Ramadan is the month of fasting, which is a deed practiced by many Muslims. Muslims fast for thirty consecutive days from sunrise to sunset, and therefore, hours of fasting change from one country to another but generally range from 10 hours to 21 hours. Fasting during this time includes all forms of food or liquids, including water. At sunset, Muslims break their fast when they start consuming meals and drinks. Ramadan is followed by a huge population in the Islamic world, leading to the importance of addressing clinical risks associated with prolonged fasting in patients with diabetes, especially when treated with SGLT2 inhibitors [17]. Here we present the first case of EDKA associated with Ramadan fasting that included a 14-hour daily fast sustained over a 30-day period while being on dapagliflozin.

Case presentation

A 51-year-old Moroccan male with past medical history of type 2 diabetes mellitus presented to the emergency department for evaluation of his acute symptoms. He complained of epigastric pain and fatigue for 3 days. He was further reported to have bouts of nonbloody, nonbilious vomiting associated with poor oral intake. He denied any chest pain, fever, or cough. He had no change in bowel habits. He reported no contact with a sick person or recent travel history. His family and psychosocial histories were unremarkable. Upon documenting his medication history, the patient was on metformin regularly for 10 years for his diabetes. Dapagliflozin 5 mg was added to metformin 1000 mg daily 12 weeks prior to presentation. The symptoms started the day following completion of Ramadan fasting over a 30-day period. Fasting from food and drinks lasted daily for approximately 14 hours daily. He broke his fast with a three-course meal, starting

with a light meal which was mainly based on fruits and fluids, a second course of protein-based items along with vegetables and carbohydrate-containing items. Finally, the meal was concluded with carbohydrate-based items. Drinks were consumed throughout the fast-breaking period.

Vital signs in the emergency department were documented as follows: Kussmaul's pattern of breathing, with a respiratory rate of 22 breaths/min and a pulse rate of 112 bpm. The patient was otherwise alert and oriented. His chest and abdominal examination were unremarkable. DKA workup, blood sugar level, venous blood gas, and urine analysis were carried out; the results are presented in Table 1.

Initial blood workup revealed a random blood glucose of 13.5 mmol/l (243 mg/dL). The venous blood gas results showed severe metabolic acidosis with a high anion gap, pH of 6.9 and PCO_2 of 20.4 mmHg with HCO_3^- of 4 mmol/L. The calculated anion gap was 30 mEq/L. Urine was positive for ketones and glucose. Based on the above presentation, euglycemic diabetic ketoacidosis was diagnosed. The patient was resuscitated with 4 L of normal saline intravenously, and insulin at a dose of 1 unit/kg was initiated.

The cause of ketoacidosis was investigated to rule out other precipitants for acidosis. Complete blood work-up showed a mild increase in white blood cells at $16.5 \times 10^9/L$ (normal range of $4.5\text{--}11.0 \times 10^9/L$) with a high neutrophil count of $14.56 \times 10^9/L$ (normal range of $1.8\text{--}7.70 \times 10^9/L$). Inflammatory markers, such as C-reactive protein, were within the normal range. Furthermore, a 12-lead electrocardiogram showed a sinus rhythm with minimal nonspecific changes in the inferior leads, which could be related to increased respiration. However, cardiac enzymes were within normal range.

Table 1 Metabolic panel

Labs	Reference range	ED	Day 1	Day 2
Random blood glucose	3.9–6.1 mmol/L (70.2–109.8 mg/dL)	13.5 (243)	6.4	115.2
Sodium	136–145 mmol/L	143	142	136
Potassium	3.4–5.1 mmol/L	4.4	3.7	3.6
Chloride	98–107 mmol/L	109	110	109
Venous blood gas				
pH		6.92	7.2	7.3
$PaCO_2$	35.0–45.0 mmHg	20.4	24.7	41.1
HCO_3^-	35.0–40.0 mmol/L	4	11	25
Anion gap	8–16 mEq/L	30	21	2
Serum lactate	0.5–2.2 mmol/L	2.50	0.7	0.6

The patient did not report any respiratory symptoms; therefore, a chest X-ray was not indicated.

He was admitted to a regular medical ward and was kept on insulin and sodium bicarbonate infusions. Metformin and dapagliflozin were not resumed. The patient's condition improved and as did his metabolic parameters (Table 1). The blood gas normalized, and the anion gap closed. His capillary blood glucose readings were optimal for the inpatient setting. The patient's insulin infusion was bridged to subcutaneous insulin. He was discharged on insulin glargine 10 units at bedtime and aspart insulin 5 units before meals.

Discussion

We report a case of euglycemic diabetic ketoacidosis triggered by prolonged fasting. To the best of our knowledge, this is the first case report of EDKA with SGLT2 inhibitor use induced by decreased caloric intake due to Ramadan fasting. It is well known that prolonged fasting (as early as 12–14 hours of fasting) will result in ketone formation. Ketone formation normally augments insulin secretion, which can decrease the rate of ketone generation; however, in diabetic patients or those who use SGLT2 inhibitors, this mechanism is affected [3, 6].

Other stressors have been briefly mentioned in literature and even as case reports, but in this case, the severity of acidosis was remarkable especially in SGLT2 inhibitor-induced EDKA.

It was challenging to arrive at a diagnosis on presentation as the patient's symptoms were generalized and could fit many differentials. However, the Kussmaul pattern of breathing and tachypnea along with history of diabetes mellitus prompted doctors to check venous blood gas to rule out acidosis. EDKA could result from multiple precipitants, but decreased oral intake is the most cited stressor for precipitating EDKA with or without SGLT2 inhibitor use [2, 3, 5, 6]. In addition, studies have shown that SGLT2 inhibitors, in general, increase the risk of DKA by sevenfold [16]. According to a report generated by the Food and Drug Administration (FDA), seventy-three cases of ketoacidosis requiring hospitalization were reported from March 2013 to May 2015 in patients with type 1 or type 2 diabetes mellitus treated with SGLT2 inhibitors; however, out of 73 cases, 40 had an average blood glucose levels of 11.7 mmol/L (211 mg/dL).

Being on a carbohydrate-deficient diet leads to a hypoglycemic effect that will result in a shift from glucose to lipid utilization for energy production. This mechanism will also increase glucagon levels and decrease insulin stimulation, promoting ketogenesis [18, 19]. The exact mechanism by which SGLT2 inhibitors precipitate the development of EDKA is not yet clear. However, the proposed pathophysiological mechanism is that SGLT2

blockers decrease blood glucose levels by increasing glycosuria and decreasing endogenous insulin secretion. In addition, they directly stimulate α -cells to produce more glucagon in response to hypoglycemia and decrease insulin secretion. As a result of this effect, more glucagon is produced, which promotes hepatic ketogenesis. Another effect of SGLT2 inhibitors is an increase in the reabsorption of acetoacetate in the renal tubules, which contributes to the increase in ketone levels in the blood [16, 20, 21].

In 2021, Tan reported three cases of EDKA in diabetic patients on SGLT2 inhibitors that were induced by a recent decrease in caloric intake [13]. In contrast, our patient fasted for 14 hours daily but then broke his fast at sunset as part of observing Ramadan while being on dapagliflozin.

Possible precipitants mentioned above were ruled out upon our patient's presentation, hence we presumed the cause of his ketoacidosis was fasting in Ramadan while being on dapagliflozin.

In 2017, a literature review described the effect of fasting for Ramadan on insulin-dependent diabetic patients. All studies concluded that there was no change but rather some improvement in glycemic control during fasting for Ramadan. Furthermore, the incidence of hyperglycemia and diabetes ketoacidosis was insignificant [22].

Similarly, a low-carbohydrate diet and an increase in fat in the diet can theoretically induce ketoacidosis [23]. There have been case reports illustrating the effect of a low-calorie diet consumed by diabetic patients while on SGLT2 inhibitors, leading to EDKA [5, 24]. In contrast, in our case, the patient had been fasting long enough where there was no intake of food and drinks for long hours. This denotes an association between fasting and the development of EDKA while on a SGLT2 inhibitor [24].

Typically, the treatment of SGLT2 inhibitor-associated EDKA is similar to the conventional DKA treatment protocol, with an emphasis on closer monitoring of capillary blood glucose levels. For this reason, our patient was fluid resuscitated and started on insulin infusion, and electrolyte disturbances were corrected [25]. Universally, as a preventative measure, it is advised to stop SGLT2 inhibitors in the setting of acute illness to decrease the risk of EDKA [26]. In clinical practice, the Australian and New Zealand Colleges of Anesthetists advocate that SGLT2 inhibitors be stopped 3 days prior to surgery or in other physically stressful situations [27].

The practice in our institution in preparation for Ramadan fasting is to educate patients on switching the time of medication intake and instruct them to take it once they break their fast. Moreover, we advise them to increase fluid intake to keep hydrated. It is of crucial importance to educate patients if they undergo any dietary changes,

such as carbohydrate restriction or being on a ketogenic diet [24].

As a recommendation, patients on SGLT2 inhibitors are advised to keep themselves hydrated, have a balanced meal, and consider stopping the medication during prolonged periods of fasting and/or in case of illness [28]. A discussion between the care provider and patient should occur before initiating a SGLT2 inhibitor. Counseling should include mentioning adverse events, especially in the setting of prolonged fast, to avoid pronounced ketone formation and acidemia. This case highlights the importance of counseling, especially in patients using SGLT2 inhibitors.

Conclusion

SGLT2 inhibitors can increase the risk of EDKA. More cases are now being reported as these medications are used in abundance in clinical practice. However, this is the first case report describing EDKA induced by prolonged fasting due to Ramadan while on a SGLT2 inhibitor. Physicians should have a high level of suspicion for EDKA if the patient is on a SGLT2 inhibitor. EDKA counseling and possible medication adjustment should be added to clinical practice in those on SGLT2 inhibitors who are decreasing caloric intake through weight-loss-directed behavioral modifications or dedicated fasting such as during the month of Ramadan.

Abbreviations

SGLT2: Sodium-glucose cotransporter 2; DKA: Diabetes ketoacidosis; EDKA: Euglycemic diabetic ketoacidosis.

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Authors' contributions

Both authors read and approved the final manuscript. AA and EA conceptualized the case report. AA obtained the consent form. AA and EA contributed to writing the case and drafting the manuscript. AA, and EA, critically revised the manuscript and approved the final submission of the manuscript.

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Availability of data and materials

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Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The authors declare that they have no competing interests.

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