

“The Bitter Truth of Sugar”—Euglycemic Diabetic Ketoacidosis due to Sodium-glucose Cotransporter-2 Inhibitors: A Case Series

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ABSTRACT

Diabetic ketoacidosis (DKA) is an acute and major complication of diabetes mellitus (DM), both type I and type II. Biochemically, DKA consists of a triad of blood sugar levels greater than 250 mg/dL, ketonemia of greater than 3 mmol/L and/or significant ketonuria, and a blood pH less than 7.3 with an increased anion gap. Currently, the sodium-glucose cotransporter-2 inhibitors (SGLT-2i) are widely used in management of type II diabetes. There have been several reports of an association between euglycemic diabetic ketoacidosis (EuDKA) and SGLT-2i agents. We present three different patients who were on SGLT-2i therapy who developed recurrent EuDKA postprocedure or sepsis. We believe that prolonged treatment (5–6 days) with intravenous (IV) insulin with glucose until resolution of glycosuria can be considered as an inexpensive marker of resolution of EuDKA. Moreover, the recommended duration for discontinuation of these drugs prior to elective procedures should be longer than 3 days.

Keywords: Euglycemia, Gliflozins, Glycosuria, High anion gap metabolic acidosis, Intensive care unit, Oral hypoglycemic agents, Sodium-glucose cotransporter-2 inhibitors.

Indian Journal of Critical Care Medicine (2022): 10.5005/jp-journals-10071-24076

INTRODUCTION

Sodium-glucose cotransporter-2 inhibitors (SGLT-2i) (gliflozins) are the newest class of oral hypoglycemic agents (OHAs) approved by the US Food and Drug Administration (FDA) for the treatment of adult-onset diabetes. Rare but serious condition of these inhibitors, reported by FDA, is diabetic ketoacidosis (DKA),¹ where plasma glucose is normal or minimally elevated, in spite of high anion gap metabolic acidosis (HAGMA) and increased plasma ketones. The prognosis of “euglycemic diabetic ketoacidosis” (EuDKA) is similar to DKA and underreported due to normoglycemia.² We describe here three cases on empagliflozin alone or in combination with other OHAs who were diagnosed with recurrent EuDKA which needed prolonged intravenous (IV) insulin therapy which resolved once glycosuria subsided.

CASE DESCRIPTIONS

Informed consent for the publication from all three patients and the approval from the institutional ethics committee (IEC) were taken (Reference: IEC Study Number: HNH/IEC/2021/CR/CCM/10).

Case 1

A 66-year-old gentleman, diagnosed with type II DM, was on empagliflozin (10 mg OD), metformin (500 mg BD), and basal-bolus therapy (regular insulin thrice a day and degludec once a day) to control his blood sugar. He presented with a history of unconsciousness, vomiting, and headache after traumatic brain injury without signs of any focal neurological deficit. Computed tomography (CT) of the brain was suggestive of subarachnoid, subdural hemorrhage with minor basal temporal fracture without cerebrospinal fluid (CSF) leak. The patient was shifted to the medical intensive care unit (ICU), OHAs were stopped, and he was treated

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How to cite this article: Shah M, Pathrose E, Bhagwat NM, Chandy D. “The Bitter Truth of Sugar”—Euglycemic Diabetic Ketoacidosis due to Sodium-glucose Cotransporter-2 Inhibitors: A Case Series. *Indian J Crit Care Med* 2022;26(1):123–126.

Source of support: Nil

Conflict of interest: None

with subcutaneous insulin therapy. He was transferred to the ward after 3 days where empagliflozin was restarted.

He was readmitted to the ICU within 24 hours in view of altered sensorium and tachypnea. Repeat CT brain was unremarkable as was the sepsis workup. His breathlessness persisted in spite of oxygen saturation and a clear chest X-ray. However, arterial blood gas (ABG) revealed a HAGMA (base excess of 20 mEq/L) with normal lactate and glucose levels but raised ketones resulting with EuDKA. Intravenous insulin was commenced as per the DKA protocol and shifted to subcutaneous insulin once the anion gap (AG) and ketones resolved after 48 hours (Table 1). Astonishingly, a relapse of HAGMA with positive serum and urine ketones with euglycemic

Table 1: Trends of various parameters guiding treatment (Case 1)

| Readmission day | Blood glucose (mg/dL) | Serum ketone (mmol/L) | Urine ketone (mg/dL) | Urine glucose | Anion gap |
|-----------------|-----------------------|-----------------------|----------------------|---------------|-----------|
| 1 | 236 | 2.6 | 160 | ++ | 20.4 |
| 2 | 123 | 0.3 | 40 | + | 13.46 |
| 3 | 145 | 0.1 | 5 | + | 9.9 |
| 4 | 186 | 3.4 | 80 | ++++ | 18.6 |
| 6 | 179 | 0.3 | 5 | + | 15.3 |
| 8 | 149 | 0.2 | TRACE | + | 14.4 |
| 10 | 128 | 0.2 | TRACE | NEGATIVE | 16 |

Table 2: CSF analysis (Case 1)

| Readmission day | WBC (cells/mL) | RBC (cells/mL) | Lactate (mg/dL) | Glucose (mg/dL) | Blood glucose (mg/dL) |
|-----------------|----------------|----------------|-----------------|-----------------|-----------------------|
| Day 10 | 920 | 20,000 | 79.2 | 49 | 110 |
| Day 14 | 242 | 1,147 | 31.8 | 72 | 108 |
| Day 22 | 18 | 760 | 27.08 | 71 | 128 |

Table 3: Case 2

| Readmission day | Blood glucose (mg/dL) | Serum ketone (mmol/L) | Urine ketone (mg/dL) | Urine glucose | Anion gap |
|-----------------|-----------------------|-----------------------|----------------------|---------------|-----------|
| 1 | 216 | 2.6 | >160 | ++ | 22.0 |
| 2 | 186 | 1.3 | 80 | ++ | 13.46 |
| 3 | 146 | 0.9 | 20 | + | 9.9 |
| 4 | 130 | 0.2 | Trace | + | 9.0 |
| 5 | 126 | 0.3 | Negative | - | 9.0 |

Table 4: Case 3

| Readmission day | Blood glucose (mg/dL) | Serum ketone (mmol/L) | Urine ketone (mg/dL) | Urine glucose | Anion gap |
|-----------------|-----------------------|-----------------------|----------------------|---------------|-----------|
| 1 | 186 | 2.8 | >160 | ++ | 16.0 |
| 2 | 176 | 1.6 | 80 | ++ | 13.46 |
| 3 | 146 | 1.4 | 40 | + | 11.0 |
| 4 | 130 | 0.8 | Trace | + | 10.0 |
| 5 | 126 | 0.3 | Negative | - | 9.9 |

was seen. The previous management with glucose and insulin continued for 10 days until glycosuria cleared.

We believe that the trigger for the EuDKA relapse, in a patient with altered sensorium and negative cultures, was likely occult infection with starvation. This was confirmed with CSF analysis (Table 2) which revealed aseptic meningitis with raised lactates, leukocytes, proteins, low sugars, and negative BioFire cultures. He was treated with meropenem and vancomycin for 21 days, and he improved to be discharged home.

Case 2

A 74-year-old gentleman, with a history of type II DM on OHAs (empagliflozin 25 mg + linagliptin 5 mg once daily) for the last 5 years, was admitted postcoronary artery bypass grafting (CABG) surgery. His OHAs were stopped and he was switched over to subcutaneous insulin 24 hours prior to the surgery.

Immediate post-CABG, the ABG was suggestive of HAGMA with normal lactates and glucose levels. Despite fluid resuscitation, adequate urine output, ketosis with subsequent ABG showing no improvement, and home medications suggesting the preoperative use of SGLT-2i, a clinical diagnosis of EuDKA was confirmed from positive serum and urine ketones. With our previous experience, we treated him with IV crystalloids, dextrose, and insulin infusion with potassium replacements until glycosuria was cleared. This took around 5 days (Table 3). The patient was improved and then switched to a regular subcutaneous insulin regimen, and SGLT-2i was discontinued.

Case 3

A 71-year-old woman, with type II DM on SGLT-2i (empagliflozin 12.5 mg once daily), was admitted with large bowel obstruction and bilateral hydronephrosis. She underwent surgery and postoperatively shifted to the surgical ICU for further monitoring and management where an ABG showed a HAGMA with normal lactates and sugar levels. On the basis of the experience of the prior two cases, EuDKA was suspected, proven, and treated accordingly until the serum ketones and glycosuria were negative in 5 days similar to Case 2 (Table 4).

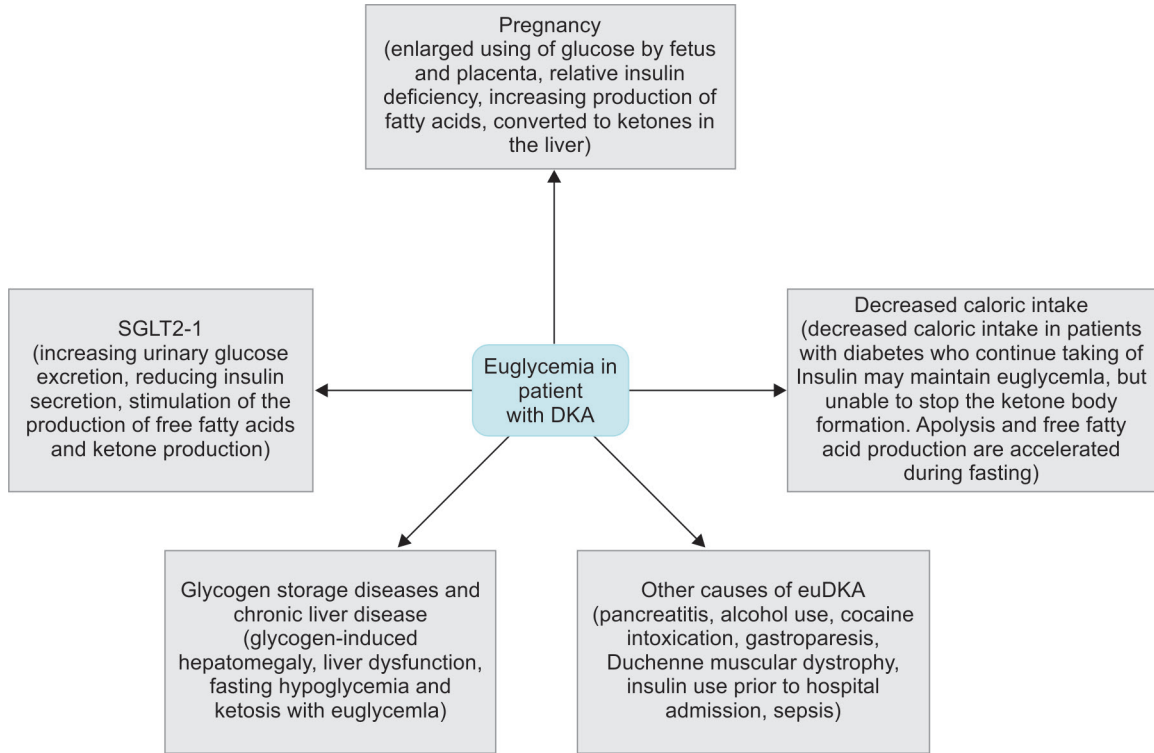
DISCUSSION

EuDKA is triggered by factors such as starvation, sepsis, post-surgery, pregnancy and SGLT-2i (Flowchart 1).³ SGLT-2i act on the SGLT-2 in the proximal tubule diminishing resorption of glucose leading to glycosuria as well as reducing the Sodium reabsorption which may contribute to dehydration.⁴ This can cause a starvation state and ketogenesis in patients on restricted carbohydrate diet and fluid intake in the presence of illness or perioperative state. With the improvement in glucose levels, patients may reduce insulin dosages that elevate the risk of ketogenesis due to beta-cell dysfunction and the reduced renal clearance of ketones.⁵ The aforementioned factors and increased glucagon release contribute to EuDKA.⁶

The factors contributing to the recurrent EuDKA in these three cases were sepsis (case 1) and surgical stress (case 2 and 3) supplemented with the presence of empagliflozin causing persistent glycosuria and ketonemia ranging between 5 and 10 days postdiscontinuation of the medication. Prolonged glycosuria and relapse of DKA related to SGLT-2i therapy were also reported.⁷ Continuous use of IV insulin therapy helped in resolving glycosuria. Considering the estimated half-life of 13.1 hours for empagliflozin, clearing glycosuria in 5 and 6 days was unexpectedly⁸ more than the FDA recommended 3 days. Case series by Wescott et al. reported 11 patients who had prolonged glycosuria and relapse of EuDKA



Flowchart 1: Triggers and mechanisms of euglycemia in patients with DKA.³ Reproduced with permission: Barski et al. 2019



as also observed with other SGLT-2i. Thus, glycosuria is an indirect marker for the presence of a drug in the body. Prolonged IV insulin and glucose supplement and withholding SGLT-2i for 6–8 days prior to an elective surgery may be considered to prevent EuDKA.^{9,10} We have enlisted common management parameters for treating DKA and EuDKA which we followed in our unit and may be helpful (Table 5).

Table 5: Difference in the management of DKA and EuDKA

| No. | Treatment | DKA | EuDKA |
|-----|--------------------------------|-----|-------|
| 1. | Hydration with isotonic saline | ++ | ++ |
| 2. | Dextrose infusion 10–25% | + | ++ |
| 3. | Potassium replacement | ++ | ++ |
| 4. | Monitoring glycosuria | – | ++ |
| 5. | Monitoring serum ketones | ++ | ++ |

CONCLUSION

The management of EuDKA requires not only the clearance of ketones or closure of AG and the clearance of glycosuria with concomitant blood sugar <160 mg/dL but also the duration of discontinuation of the drug prior to elective procedure.

ACKNOWLEDGMENT

The authors acknowledge the extraordinary work and valuable suggestions of Ms Kavita Shalia, PhD, Sr Scientist, for drafting the manuscript.

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