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CASE REPORT

# A Case Report on Dapagliflozin-Associated Euglycemic Diabetic Ketoacidosis Triggered by Acute Viral Gastroenteritis

Syed Afzal Uddin Biyabani*[1], Zunera Fatima[2], Vanishree P Babladi[3], Pooja V Salimath[4], Chandrika C[5], Hafsa Naema[6], Safa Wasay[7]

[1] *Research Scholar, Department of Pharmacy Practice, Rajiv Gandhi University of Health Sciences, Kalaburagi, Karnataka, India*
[2] *PharmD Graduate, Department of Pharmacy Practice, Deccan School of Pharmacy, Hyderabad, Telangana, India*
[3] *Assistant Professor, Department of Pharmacy Practice, Matoshree Taradevi Institute of Pharmaceutical Sciences, Kalaburagi, Karnataka, India*
[4] *Associate Professor & Research Scholar, Department of Pharmacy Practice, Matoshree Taradevi Rampure Institute of Pharmaceutical Sciences, Kalaburagi, Karnataka, India*
[5] *Assistant Professor, Department of Pharmacy Practice, Visveswarapura Institute of Pharmaceutical Sciences, Bangalore, India*
[6] *PharmD Graduate, Dept. of Pharmacy Practice, Matoshree Taradevi Rampure Institute of Pharmaceutical Sciences, Kalaburagi, Karnataka, India*
[7] *PharmD Scholar, Dept. of Pharmacy Practice, Jawaharlal Nehru Technological University, Hyderabad, Telangana, India*

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**Abstract**: Sodium-glucose cotransporter-2 (SGLT2) inhibitors represent a cornerstone in the modern management of type 2 diabetes mellitus, offering substantial benefits beyond glycemic control, including significant reduction in cardiovascular mortality and slowing the progression of chronic kidney disease. However, the emergence of euglycemic diabetic ketoacidosis (EDKA) as a rare but life-threatening complication poses a diagnostic challenge for clinicians. Unlike the traditional presentation of diabetic ketoacidosis, EDKA is characterized by severe metabolic acidosis and ketonemia in the presence of near-normal or only mildly elevated blood glucose levels, often leading to delayed recognition and intervention. A 52-year-old male with a twelve-year history of type 2 diabetes mellitus presented to the emergency department with symptoms of profound dehydration, nausea, and abdominal pain following a brief period of acute viral gastroenteritis and reduced oral intake. Despite a serum glucose concentration of 186 mg/dL, laboratory findings confirmed a high-anion-gap metabolic acidosis (pH 7.2, bicarbonate 12 mmol/L) and significant ketosis (β-hydroxybutyrate 7.1 mmol/L). The patient had been consistently using 10 mg of dapagliflozin daily. Clinical recovery was achieved through the immediate cessation of the SGLT2 inhibitor, aggressive fluid resuscitation, and a specialized protocol involving concurrent insulin and dextrose infusions to resolve the acid-base imbalance while maintaining normoglycemia. This case shows the necessity of "sick-day" education for patients on SGLT2 inhibitors and the need for mandatory ketone assessment in any diabetic patient presenting with systemic illness, regardless of blood glucose levels.

**Keywords:** SGLT2 Inhibitors; Dapagliflozin; Euglycemic Diabetic Ketoacidosis; Metabolic Acidosis; Ketogenesis.

## 1. Introduction

Type 2 diabetes mellitus (T2DM) is one of the most significant global health crises of the 21st century, characterized by peripheral insulin resistance and a progressive decline in pancreatic β-cell function. This metabolic dysregulation leads to chronic hyperglycemia and a cascade of macrovascular and microvascular complications [1]. Current epidemiological data indicate that the prevalence of T2DM is increasing at an alarming rate, particularly in low- and middle-income regions, necessitating robust and multifaceted therapeutic strategies to mitigate long-term morbidity and mortality [2]. The therapeutic management for T2DM has been revolutionized by the introduction of sodium-glucose cotransporter-2 (SGLT2) inhibitors, such as dapagliflozin, empagliflozin, and canagliflozin. These agents function through a unique, insulin-independent mechanism by targeting the SGLT2 proteins in the proximal convoluted tubules of the kidneys [3]. These medications prevent the reabsorption of approximately 90% of filtered glucose by inhibiting these transporters, thereby promoting significant glucosuria and effectively lowering plasma glucose concentrations [4]. Apart from glucose-lowering effects, SGLT2 inhibitors exert favorable pleiotropic effects, including modest blood pressure reduction through osmotic diuresis and weight loss via caloric loss in the urine [5]. Large-scale clinical trials have firmly established the role of SGLT2 inhibitors in reducing the risk of hospitalization for heart failure and cardiovascular-related death [6]. Their renoprotective properties have made them a first-line recommendation for patients with diabetic kidney disease, as they effectively reduce intraglomerular pressure and stabilize the estimated glomerular filtration rate over time [7]. International guidelines have prioritized their use in patients with established atherosclerotic cardiovascular disease or high cardiovascular risk [8].

* Corresponding author: Syed Afzal Uddin Biyabani

Despite the undeniable clinical benefits, the safety profile of SGLT2 inhibitors includes several specific risks, ranging from mycotic genital infections to more severe metabolic disturbances [9]. Euglycemic diabetic ketoacidosis (EDKA) is perhaps the most clinically deceptive complication. While classical diabetic ketoacidosis (DKA) is defined by the triad of hyperglycemia (usually >250 mg/dL), ketosis, and metabolic acidosis, EDKA presents with the latter two features despite blood glucose levels remaining below 250 mg/dL or even within the normal range [10, 11]. This atypical biochemistry frequently masks the severity of the patient's condition, as healthcare providers may falsely equate near-normal glucose levels with metabolic stability.

## 2. Case Presentation

### 2.1. Patient History and Presentation

A 52-year-old male with a 12-year history of T2DM was admitted to the emergency department experiencing persistent nausea, projectile vomiting, and generalized malaise that had escalated over a 72-hour period. His symptoms were preceded by an episode of acute viral gastroenteritis, which resulted in significant anorexia and poor fluid intake. His medical history was significant for hypertension and dyslipidemia, both managed for several years. He denied any history of alcohol abuse, recent surgical procedures, or previous episodes of ketoacidosis. His outpatient regimen consisted of metformin (1000 mg twice daily), dapagliflozin (10 mg once daily), telmisartan (40 mg once daily), and rosuvastatin (20 mg once daily).

**Table 1. Medication History of the Patient**

| Medication | Class | Dosage | Frequency | Indication |
|---|---|---|---|---|
| Dapagliflozin | SGLT2 Inhibitor | 10 mg | Once Daily | Type 2 Diabetes Mellitus |
| Metformin | Biguanide | 1000 mg | Twice Daily | Type 2 Diabetes Mellitus |
| Telmisartan | ARB | 40 mg | Once Daily | Hypertension |
| Rosuvastatin | HMG-CoA Reductase Inhibitor | 20 mg | Once Daily | Dyslipidemia |

### 2.2. Physical Examination and Hemodynamic Status

Upon initial assessment, the patient appeared clinically distressed and moderately dehydrated, evidenced by dry buccal mucosa and decreased skin turgor. His hemodynamic profile indicated a compensatory state, with a heart rate of 108 beats per minute and a respiratory rate of 26 breaths per minute, characterized by deep, rhythmic Kussmaul breathing. His blood pressure was 102/64 mmHg, and his temperature was 36.8 °C. Abdominal examination revealed generalized tenderness without evidence of peritonitis or localized organomegaly.

### 2.3. Diagnostic Evaluation and Laboratory Findings

Initial biochemical analysis revealed a blood glucose level of 186 mg/dL, which initially appeared reassuring in the context of a diabetic emergency. However, arterial blood gas analysis showed a significant metabolic derangement with a pH of 7.20 and a serum bicarbonate level of 12 mmol/L.

**Table 2. Baseline Clinical and Biochemical Parameters upon Admission**

| Parameter | Patient Value | Reference Range | Interpretation |
|---|---|---|---|
| Blood Glucose | 186 mg/dL | 70–140 mg/dL | Mild Hyperglycemia |
| Arterial pH | 7.20 | 7.35–7.45 | Severe Acidemia |
| Serum Bicarbonate ($HCO_3^-$) | 12 mmol/L | 22–28 mmol/L | Metabolic Acidosis |
| Anion Gap | 26 mmol/L | 8–16 mmol/L | High Anion Gap |
| Serum β-hydroxybutyrate | 7.1 mmol/L | <0.4 mmol/L | Severe Ketonemia |
| Serum Creatinine | 1.3 mg/dL | 0.6–1.2 mg/dL | Mild Acute Kidney Injury |
| Urine Ketones | 3+ | Negative | Significant Ketonuria |
| Urine Glucose | 3+ | Negative | Glycosuria |

The calculated anion gap was markedly widened at 26 mmol/L (reference range: 8–16 mmol/L). Serum creatinine was slightly elevated at 1.3 mg/dL, suggesting stage 1 acute kidney injury likely secondary to volume depletion. Urinalysis was strongly positive for both glucose (3+) and ketones (3+). The diagnosis of EDKA was definitively confirmed by a serum β-hydroxybutyrate level of 7.1 mmol/L, indicating severe ketonemia despite the lack of profound hyperglycemia.

### 2.4. Acute Therapeutic Intervention

The management protocol was initiated immediately upon diagnosis. Dapagliflozin and metformin were suspended. The patient received rapid volume expansion with isotonic saline to restore circulatory volume and improve renal perfusion. A continuous intravenous insulin infusion was started at a rate of 0.1 units/kg/hour. Because the initial blood glucose was not significantly elevated, intravenous 5% dextrose was co-administered with the insulin infusion once glucose levels dropped below 200 mg/dL. This strategy was employed to provide a substrate for insulin to suppress ongoing lipolysis and hepatic ketogenesis without inducing hypoglycemia. Potassium levels were monitored hourly and supplemented to maintain concentrations between 4.0 and 5.0 mmol/L, preventing the shift-induced hypokalemia associated with insulin therapy.

**Table 3. Management Protocol for SGLT2i-Associated EDKA**

| Management Phase | Intervention | Clinical Objective |
|---|---|---|
| Phase 1: Resuscitation | Isotonic Saline (0.9% NaCl) | Restore intravascular volume and renal perfusion. |
| Phase 2: Metabolic Fix | IV Insulin Infusion (0.1 U/kg/hr) | Halt lipolysis and suppress hepatic ketogenesis. |
| Phase 3: Normoglycemia | Concurrent 5% or 10% Dextrose | Prevent hypoglycemia while maintaining insulin drive. |
| Phase 4: Electrolytes | Potassium ($K^+$) Supplementation | Prevent hypokalemia during pH correction. |
| Phase 5: Resolution | Transition to Subcutaneous Insulin | Occurs once anion gap closes and pH >7.3. |

## 3. Discussion

### 3.1. Mechanisms of SGLT2i-Induced EDKA

#### *3.1.1. The Insulin-to-Glucagon Imbalance*

The fundamental mechanism underlying EDKA in the context of SGLT2 inhibition is a profound alteration in the hormonal milieu, specifically the ratio of insulin to glucagon. By promoting significant glucosuria, these agents lower the circulating plasma glucose, which leads to a physiological reduction in endogenous insulin secretion from pancreatic β-cells [12]. Simultaneously, SGLT2 inhibitors appear to exert a direct stimulatory effect on pancreatic α-cells, which express SGLT2 transporters, leading to an increase in glucagon secretion [13, 14]. This state of relative insulinopenia combined with hyperglucagonemia mimics a starvation-like state, shifting the body's metabolic furnace from carbohydrate oxidation to fatty acid oxidation.

#### *3.1.2. Ketogenesis and Reduced Clearance*

The hormonal shift activates hormone-sensitive lipase in adipose tissue, resulting in a surge of free fatty acids (FFAs) delivered to the liver. In the hepatic mitochondria, these FFAs undergo β-oxidation to produce acetyl-CoA, which is subsequently converted into ketone bodies, namely acetoacetate and β-hydroxybutyrate [15]. SGLT2 inhibitors may decrease the renal clearance of ketone bodies, effectively raising their concentration in the blood even further [16]. Because SGLT2 inhibitors continue to promote glucose excretion through the kidneys, the intravascular glucose levels remain deceptively low, preventing the high osmotic pressure typically seen in classic DKA while the underlying ketoacidosis continues to worsen.

### 3.2. Precipitating Factors and the Metabolic Trigger

In the current case, the patient's acute viral gastroenteritis served as the definitive metabolic trigger. During periods of acute illness, the body releases counter-regulatory hormones, including cortisol, catecholamines, and growth hormone, all of which antagonize insulin action and further promote lipolysis and ketogenesis [17]. When combined with the poor oral intake and dehydration associated with gastroenteritis, the patient entered a state of profound negative energy balance. The continued use of dapagliflozin during this "sick" period exacerbated the glucosuria, preventing the body from mounting a hyperglycemic response that might have otherwise alerted the clinician to the developing metabolic crisis [18].

### 3.3. Diagnostic Challenges

The primary danger of EDKA lies in its subtle presentation. Traditional screening for DKA often relies on a high capillary blood glucose reading as the initial "red flag." In the absence of hyperglycemia, many clinicians may misattribute the patient's symptoms (nausea, vomiting, abdominal pain) to the primary illness, such as simple gastroenteritis or food poisoning [19]. This case shows that the absence of significant hyperglycemia must not be used to rule out ketoacidosis in patients on SGLT2 inhibitors. Measurement of the anion gap and direct testing for serum β-hydroxybutyrate are essential for an accurate diagnosis [20].

Relying solely on urine ketones can also be misleading, as urine dipsticks primarily detect acetoacetate rather than β-hydroxybutyrate, the predominant ketone in EDKA [21].

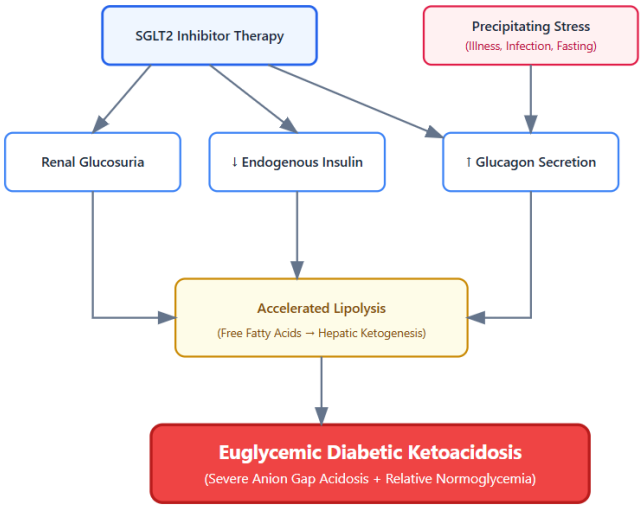


**Figure 1. Pathogenesis of SGLT2i-Associated EDKA**

**Table 4. Comparison of Classic DKA vs. Euglycemic DKA (EDKA)**

| Feature | Classic Diabetic Ketoacidosis | Euglycemic Diabetic Ketoacidosis |
|---|---|---|
| Blood Glucose | Typically >250 mg/dL | <250 mg/dL (often near-normal) |
| Anion Gap | High | High |
| Primary Trigger | Insulin deficiency/Non-compliance | SGLT2i, Starvation, Pregnancy, Liver Disease |
| Glucosuria | Present (Secondary to hyperglycemia) | Present (Secondary to SGLT2 inhibition) |
| Dehydration | Usually Severe | Moderate to Severe |
| Recognition | Rapid (Triggered by high glucose) | Often Delayed (Glucose-dependent screening) |

### 3.4. Principles of Management and Recovery

The management of EDKA requires a nuanced approach that differs slightly from standard DKA protocols. While fluid resuscitation remains the priority, the use of dextrose-containing fluids must be initiated much earlier [22, 23].

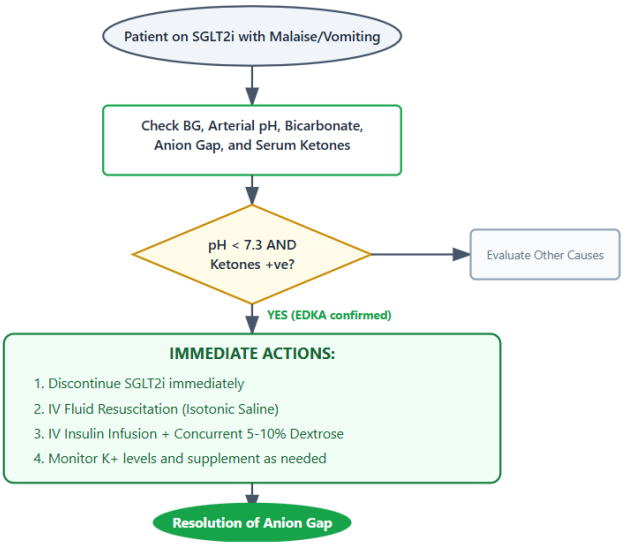


**Figure 2. Diagnosis and Treatment for EDKA**

Since the blood glucose is often near-normal, insulin cannot be administered safely without concurrent dextrose to prevent hypoglycemia. The goal of insulin therapy in EDKA is not merely to lower glucose, but to "turn off" the ketogenic pathway in the liver [24]. This patient's recovery within 36 hours illustrates the efficacy of this combined approach. The transition to subcutaneous insulin should only occur once the anion gap has closed and the patient can tolerate oral intake [25].

### 3.5. Preventive Measures and the "Sick-Day" Protocol

Prevention of EDKA necessitates comprehensive patient education. The Association of British Clinical Diabetologists and other international bodies have advocated for the "SADMANS" mnemonic or similar sick-day rules, which advise the temporary cessation of SGLT2 inhibitors (along with other medications like ACE inhibitors and metformin) during periods of acute illness, dehydration, or before major surgery [26, 27]. Patients should be counseled to recognize early warning signs such as rapid breathing or unexplained abdominal pain and to seek medical attention immediately if these occur while taking an SGLT2 inhibitor [28].

**Table 5. The "Sick-Day" Guidance for Patients on SGLT2 Inhibitors**

| Condition/Scenario | Action for SGLT2 Inhibitor | Rationale |
|---|---|---|
| Acute Gastroenteritis | Withhold Medication | Risk of volume depletion and starvation ketosis. |
| Major Surgery | Stop 3-4 days prior | Prevents perioperative metabolic acidosis. |
| Severe Infection/Sepsis | Withhold Medication | High levels of counter-regulatory hormones increase risk. |
| Prolonged Fasting | Withhold Medication | Prevents shift to fatty acid metabolism. |
| Resumption | Restart once eating/drinking | Ensures metabolic stability and adequate hydration. |

## 4. Conclusion

This case serves as a critical reminder of the metabolic complexities introduced by SGLT2 inhibitor therapy. While these medications provide indispensable benefits for cardiovascular and renal health, their potential to induce euglycemic diabetic ketoacidosis requires constant vigilance. The diagnosis must be aggressively pursued in any patient on SGLT2 inhibitors who presents with systemic symptoms, even when blood glucose levels are within a normal or near-normal range. Early recognition through the assessment of the anion gap and serum ketones, followed by a management strategy that prioritizes the suppression of ketogenesis through concurrent insulin and dextrose administration, is vital for preventing the severe morbidity associated with this condition. Clinicians must prioritize patient education regarding the suspension of these agents during acute illness to minimize the risk of this life-threatening metabolic emergency.

## Compliance with ethical standards

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*Conflict of interest statement*

The authors declare that they have no conflicts of interest or competing interests regarding the publication of this manuscript, or any financial or personal relationships with institutions or products mentioned in the study.

*Statement of ethical approval*

Ethical approval (IEC/RGUHS/2025/115) for this case report was obtained from the Institutional Ethics Committee. The study was conducted in accordance with the ethical standards of the institutional research committee and with the principles of the Declaration of Helsinki.

*Statement of informed consent*

Informed consent was obtained from the patient included in the study.

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