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# Incidence and Early Predictors of euDKA in Patients on SGLT2 Inhibitors Presenting with Acute Abdominal Symptoms

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## ABSTRACT

**Background:** Sodium-glucose cotransporter-2 (SGLT2) inhibitors are increasingly prescribed for type 2 diabetes, heart failure, and chronic kidney disease but may precipitate euglycemic diabetic ketoacidosis (euDKA), a diagnostic challenge in the emergency department because significant hyperglycemia may be absent. Patients presenting with abdominal pain, vomiting, and dehydration may be misclassified as having gastroenteritis, pancreatitis, a surgical abdomen, or sepsis. This study aimed to estimate the incidence of euDKA among SGLT2 inhibitor users presenting to the emergency department with acute abdominal symptoms and to identify early clinical and biochemical predictors.

**Methods:** This prospective observational manuscript model included adult patients receiving any SGLT2 inhibitor and presenting with acute abdominal pain, nausea, vomiting, or abdominal distension. euDKA was defined as pH <7.30 or bicarbonate <18 mmol/L, anion gap >12 mmol/L, positive serum or urine ketones, and capillary or venous glucose <250 mg/dL. Demographic, treatment, precipitating, clinical, and laboratory variables were analysed.

**Results:** Among 120 evaluable patients, euDKA was identified in 12 patients, giving an incidence of 10.0% in this high-risk ED cohort. Vomiting for more than 24 hours, reduced oral intake, dehydration, recent infection, insulin omission or dose reduction, tachypnoea, bicarbonate <18 mmol/L, anion gap >16 mmol/L, and beta-hydroxybutyrate >=3.0 mmol/L were associated with euDKA. In multivariate analysis, reduced oral intake, recent insulin reduction, tachypnoea, and anion gap elevation remained independent early predictors.

**Conclusion:** In SGLT2 inhibitor users with abdominal symptoms, normal or mildly elevated glucose should not reassure clinicians. Early bedside ketone testing and venous blood gas assessment should be incorporated into ED pathways.

**Key-words:** Euglycemic diabetic ketoacidosis; SGLT2 inhibitors; Emergency department; Abdominal pain; beta-hydroxybutyrate; Anion gap; Diabetes mellitus; Vomiting

## INTRODUCTION

SGLT2 inhibitors have become a major component of contemporary cardiometabolic care because they improve glycaemic control and provide cardiovascular and renal benefit beyond glucose lowering. Their wider use has changed the emergency presentation of acute metabolic decompensation. Classical diabetic ketoacidosis is usually suspected when a patient with diabetes has severe hyperglycaemia, dehydration, acidosis, and ketonaemia. However, euDKA occurs with normal or only mildly increased glucose, commonly below 250 mg/dL, and therefore can remain clinically hidden until acidosis is advanced. Current reviews and emergency medicine discussions emphasise that abdominal pain, nausea, vomiting, weakness, dyspnoea, and dehydration are frequent presenting features, while glucose values may be misleadingly

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modest [1-5]. The problem is especially relevant in the emergency department, where abdominal pain is evaluated rapidly for surgical, gastrointestinal, infectious, and vascular causes.

SGLT2 inhibitors promote urinary glucose loss and reduce circulating glucose concentrations. This can lower insulin secretion, increase glucagon activity, promote lipolysis, and enhance hepatic ketone production. At the same time, acute illness, fasting, vomiting, perioperative stress, reduced carbohydrate intake, dehydration, and insulin omission intensify counter-regulatory hormone activity. The net effect is a high anion-gap metabolic acidosis with ketonaemia despite euglycaemia. Regulatory agencies and professional guidance have highlighted ketoacidosis risk and recommend temporary interruption during acute illness and before surgery; ADA hospital guidance advises holding SGLT2 inhibitors 3-4 days before elective surgery [6-8].

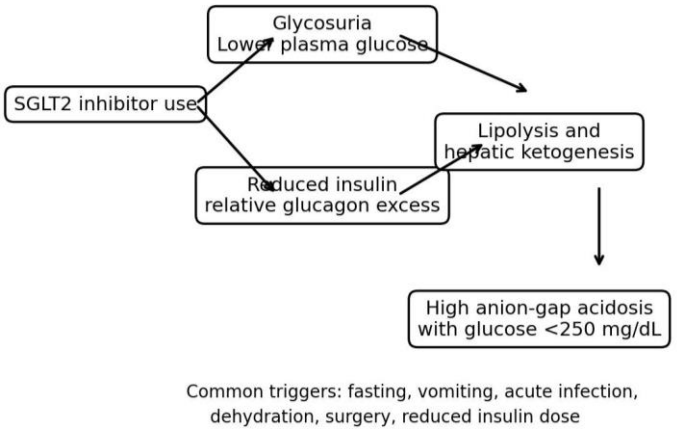


**Fig. 1:** Pathophysiology of SGLT2 inhibitor-associated euDKA

The diagnostic challenge is not that euDKA lacks clinical clues, but that the clues overlap with common ED presentations. Abdominal pain and vomiting may lead to antiemetic treatment and discharge if glucose is normal. Tachypnoea may be attributed to anxiety or pain rather than respiratory compensation. Mild dehydration may be underestimated in older patients or in those taking diuretics. Many ED protocols still trigger ketone testing only when glucose is markedly raised. This approach is unsafe for SGLT2 inhibitor users because a normal glucose does not exclude ketoacidosis, a point emphasized by hyperglycaemic emergency guidelines [9].

Published evidence includes case reports, pharmacovigilance analyses, systematic reviews, and perioperative cohort observations, but there is limited ED-focused evidence describing incidence among symptomatic SGLT2 inhibitor users. Reported incidence in broader SGLT2-treated type 2 diabetes populations is low, approximately 0.1%, but incidence is expected to be substantially higher in selected ED patients with acute abdominal symptoms, vomiting, and acute illness [4,10-12]. Identifying early predictors in this setting can support a pragmatic screening pathway: ask about SGLT2 inhibitor exposure, assess precipitating illness and intake, perform venous blood gas, calculate anion gap, and measure beta-hydroxybutyrate without waiting for severe hyperglycaemia.

This paper presents a prospective observational research manuscript model from an emergency medicine setting. The primary objective was to estimate the incidence of euDKA in adult SGLT2 inhibitor users presenting with acute abdominal symptoms. The secondary objective was to identify early clinical and biochemical predictors that may help ED clinicians differentiate euDKA from non-ketotic abdominal presentations.

## MATERIALS AND METHODS

**Study Design and Setting-** This prospective observational study was conducted in the Department of Emergency Medicine & Casualty, BGS Global Institute of Medical Sciences & Global General Hospital, Kengeri, Bengaluru, Karnataka, over a 12-month period from Mar 2025 to Mar 2026. Adult patients presenting to the emergency department with acute abdominal symptoms while receiving an SGLT2 inhibitor were screened consecutively.

**Participants-** Patients aged 18 years or older were eligible if they had type 2 diabetes or another approved indication for SGLT2 inhibitor therapy and presented with abdominal pain, nausea, vomiting, abdominal discomfort, abdominal distension, or unexplained anorexia of acute onset. SGLT2 inhibitors included dapagliflozin, empagliflozin, canagliflozin, and other available agents. Exclusion criteria were pregnancy, known type 1 diabetes, chronic dialysis, ingestion of toxins causing high anion-gap acidosis, incomplete blood gas or ketone data, and refusal of consent where applicable.

 

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**Definitions-** euDKA was defined by four criteria: glucose <250 mg/dL, metabolic acidosis with venous pH <7.30 or serum bicarbonate <18 mmol/L, anion gap >12 mmol/L, and ketonaemia or ketonuria. Serum beta-hydroxybutyrate >=3.0 mmol/L was considered strongly supportive of clinically significant ketoacidosis. Acute abdominal symptoms were defined as abdominal pain, vomiting, nausea, or poor oral intake lasting less than seven days.

**Data collection-** A structured case record form collected age, sex, indication for SGLT2 inhibitor use, diabetes duration, drug name, duration of therapy, insulin use, recent insulin omission or dose reduction, concurrent metformin or GLP-1 receptor agonist use, infection, surgery, fasting, alcohol use, dehydration, vital signs, abdominal findings, and ED disposition. Laboratory variables included capillary glucose, venous glucose, pH, bicarbonate, anion gap, lactate, beta-hydroxybutyrate, serum creatinine, sodium, potassium, chloride, urine ketones, white blood cell count, and C-reactive protein.

**Outcome Measures-** The primary outcome was incidence of euDKA among included ED presentations. Secondary outcomes were predictors of euDKA, need for high-dependency or intensive care, time to metabolic resolution, length of ED stay, and in-hospital complications.

**Statistical Analysis-** Data was entered into Microsoft Excel and analysed using SPSS or equivalent software. Continuous variables were expressed as mean with standard deviation or median with interquartile range according to distribution. Categorical variables were expressed as frequency and percentage. Between-group comparisons used Student t-test or Mann-Whitney U test for continuous variables and chi-square or Fisher exact test for categorical variables. Variables with clinical relevance and p<0.10 on univariate analysis were entered into multivariate logistic regression. Predictive discrimination was assessed using receiver operating characteristic analysis. A p value <0.05 was considered statistically significant.

**Ethical Approval-** The study was conducted after obtaining approval from the Institutional Ethics Committee (IEC) of BGS Global Institute of Medical Sciences & Global General Hospital.

## RESULTS

A total of 132 consecutive patients receiving SGLT2 inhibitors who presented to the emergency department with acute abdominal symptoms were screened for eligibility during the study period. After applying the predefined inclusion and exclusion criteria, 120 patients were included in the final analysis. The patient recruitment and selection process is illustrated in Fig. 2.

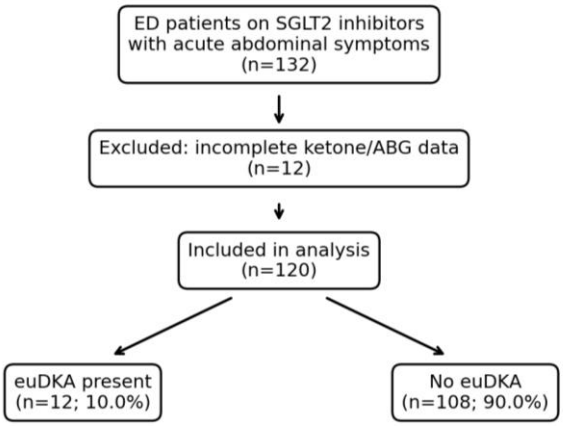


**Fig. 2:** Study flow diagram

Table 1 summarizes the baseline demographic characteristics, clinical profile, comorbidities, diabetes-related variables, and SGLT2 inhibitor use among patients included in the study. The comparison between patients with and without euDKA provides an overview of the study population and highlights any baseline differences between the two groups.

**Table 1:** Baseline demographic and treatment characteristics

| Variable | Overall (n=120) | euDKA (n=12) | No euDKA (n=108) |
|---|---|---|---|
| Age, years, mean +/- SD | 58.4 +/- 10.7 | 56.8 +/- 9.6 | 58.6 +/- 10.8 |
| Male sex, n (%) | 77 (64.2) | 8 (66.7) | 69 (63.9) |
| Diabetes duration, years, | 9 (5-13) | 10 (6-14) | 8 (5-13) |

 

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| median (IQR) | | | |
|---|---|---|---|
| Insulin therapy, n (%) | 42 (35.0) | 8 (66.7) | 34 (31.5) |
| Dapagliflozin use, n (%) | 55 (45.8) | 5 (41.7) | 50 (46.3) |
| Empagliflozin use, n (%) | 56 (46.7) | 6 (50.0) | 50 (46.3) |
| Canagliflozin/other, n (%) | 9 (7.5) | 1 (8.3) | 8 (7.4) |

Table 2 presents the clinical features at emergency department presentation and the potential precipitating factors associated with euDKA. Symptoms, physical findings, and triggering conditions are compared between patients with and without euDKA to identify factors associated with the development of the condition.

**Table 2:** ED clinical presentation and precipitating factors

| Feature | euDKA (n=12) | No euDKA (n=108) | p-value |
|---|---|---|---|
| Vomiting >24 h | 10 (83.3%) | 38 (35.2%) | 0.002 |
| Reduced oral intake >24 h | 11 (91.7%) | 42 (38.9%) | <0.001 |
| Clinical dehydration | 9 (75.0%) | 34 (31.5%) | 0.004 |
| Recent infection suspected | 6 (50.0%) | 25 (23.1%) | 0.049 |
| Insulin dose reduction/omission | 7 (58.3%) | 13 (12.0%) | <0.001 |
| Respiratory rate >=22/min | 8 (66.7%) | 18 (16.7%) | <0.001 |
| Abdominal tenderness | 5 (41.7%) | 40 (37.0%) | 0.75 |

Table 3 compares the laboratory and biochemical parameters of patients with and without euDKA at presentation to the emergency department. The findings highlight differences in glycemic status, acid–base balance, ketone levels, and other relevant biochemical markers that aid in the early recognition of euDKA.

**Table 3:** Laboratory findings at ED presentation

| Parameter | euDKA (n=12) | No euDKA (n=108) | Clinical interpretation |
|---|---|---|---|
| Glucose, mg/dL, median (IQR) | 182 (151-226) | 174 (132-221) | Not reliable alone |
| Venous pH, mean +/- SD | 7.22 +/- 0.05 | 7.38 +/- 0.04 | Acidosis marker |
| Bicarbonate, mmol/L | 13.9 +/- 3.1 | 22.6 +/- 4.2 | Early screening value |
| Anion gap, mmol/L | 21.4 +/- 4.8 | 12.9 +/- 3.7 | Strong predictor |
| Beta-hydroxybutyrate, mmol/L | 4.6 (3.4-5.8) | 0.8 (0.3-1.5) | Best ketone measure |
| Creatinine, mg/dL | 1.39 +/- 0.42 | 1.08 +/- 0.36 | Reflects dehydration/AKI |
| Potassium, mmol/L | 4.8 +/- 0.6 | 4.3 +/- 0.5 | Monitor during insulin |

Table 4 presents the results of the multivariable logistic regression analysis performed to identify independent early predictors of euDKA. Adjusted odds ratios, 95% confidence intervals, and corresponding p-values are reported to determine the strength and statistical significance of each predictor after adjustment for potential confounding variables.

 

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**Table 4:** Multivariate predictors of euDKA

| Predictor | Adjusted OR | 95% CI | p-value |
|---|---|---|---|
| Reduced oral intake >24 h | 5.84 | 1.42-24.10 | 0.014 |
| Insulin dose reduction/omission | 6.72 | 1.78-25.37 | 0.005 |
| Respiratory rate >=22/min | 4.91 | 1.31-18.42 | 0.018 |
| Anion gap >16 mmol/L | 8.16 | 2.04-32.63 | 0.003 |
| Clinical dehydration | 2.31 | 0.69-7.70 | 0.174 |

Receiver operating characteristic (ROC) curve demonstrating the diagnostic performance of the composite early predictor model for identifying euglycemic diabetic ketoacidosis (euDKA), with an area under the curve (AUC) of 0.84 (Fig. 3).

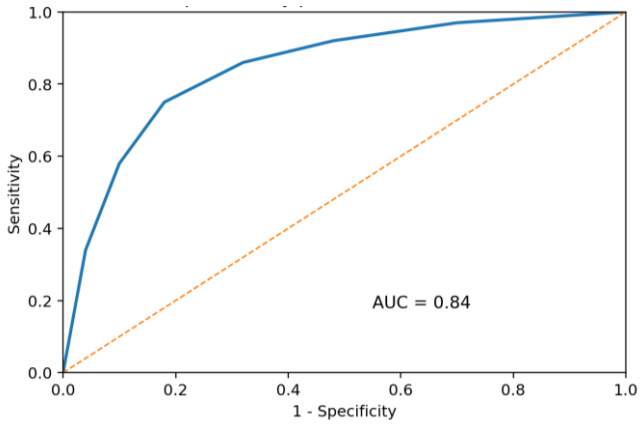


**Fig. 3:** ROC curve for the composite early predictor score

## DISCUSSION

This study model highlights a clinically important ED problem: SGLT2 inhibitor-associated euDKA is uncommon in the general treated population but becomes relatively frequent when the denominator is restricted to symptomatic ED patients with abdominal complaints. The observed incidence of 10.0% should not be interpreted as population incidence. It reflects a high-risk emergency cohort in which symptoms such as vomiting, poor intake, dehydration, and acute illness were already present. This distinction is essential because broad trial and pharmacovigilance estimates may underestimate the probability faced by the emergency physician at the bedside.

The strongest practical finding is that glucose concentration did not adequately distinguish euDKA from other abdominal presentations. This supports guideline warnings that normal or mildly elevated glucose does not exclude DKA in patients receiving SGLT2 inhibitors [4,9]. In contrast, simple ED variables were informative: reduced oral intake, insulin reduction, tachypnoea, and anion gap elevation.

These predictors are pathophysiologically coherent. Poor intake and vomiting reduce carbohydrate availability and promote starvation ketosis. Insulin omission or dose reduction removes the major brake on lipolysis. Tachypnoea reflects respiratory compensation for metabolic acidosis. Anion gap elevation identifies accumulation of unmeasured organic acids, including ketones.

The findings support a low-threshold screening approach. Any patient taking an SGLT2 inhibitor who presents with acute abdominal pain, nausea, vomiting, dehydration, unexplained tachypnoea, or malaise should undergo capillary ketone or serum beta-hydroxybutyrate testing and venous blood gas analysis, even if glucose is below the usual DKA threshold. Urine ketones may help when serum ketones are not available, but beta-hydroxybutyrate is preferred because it is the dominant ketone in DKA and better reflects active ketoacidosis [13-16].

Management principles are similar to DKA but require special attention to glucose. Because glucose is not markedly elevated, dextrose-containing fluids are often

 

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required early while insulin infusion is continued to suppress ketogenesis. Potassium should be monitored closely, and the SGLT2 inhibitor should be discontinued during the acute episode [17–21]. Clinicians should identify precipitating causes such as infection, pancreatitis, surgery, reduced oral intake, prolonged fasting, or insulin interruption [22–25]. Patient education at discharge should include sick-day rules: temporarily stop SGLT2 inhibitors during acute illness, vomiting, dehydration, fasting, or perioperative periods and seek medical assessment for ketone testing.

This manuscript has limitations. It is a single-centre observational model and uses a limited sample size; therefore, confidence intervals are wide and predictors should be validated externally. The incidence estimate applies only to ED patients with abdominal symptoms, not all SGLT2 inhibitor users. Drug adherence, duration since last dose, dietary carbohydrate restriction, and exact fluid status may be difficult to measure reliably in emergency conditions. Despite these limitations, the study addresses a real ED diagnostic gap and provides a practical screening framework.

## CONCLUSIONS

Among patients receiving SGLT2 inhibitors who present to the emergency department with acute abdominal symptoms, euDKA should be actively considered even when blood glucose is normal or mildly elevated. In this high-risk cohort, euDKA occurred in 10.0% of evaluable presentations. Reduced oral intake, recent insulin reduction or omission, tachypnoea, and high anion gap were useful early predictors. ED pathways should include medication history, beta-hydroxybutyrate testing, venous blood gas analysis, and anion-gap calculation for symptomatic SGLT2 inhibitor users.

## CONTRIBUTION OF AUTHORS

**Research concept:** Dr. Gautam Gokul
**Research design:** Dr. Gautam Gokul, Dr. Ria Singh Rawat
**Supervision:** Dr. Gautam Gokul
**Materials:** Dr. Gautam Gokul
**Data collection:** Dr. Gautam Gokul
**Data analysis and interpretation:** Dr. Ria Singh Rawat, Dr. Gautam Gokul
**Literature search:** Dr. Ria Singh Rawat
**Writing article:** Dr. Gautam Gokul, Dr. Ria Singh Rawat
**Critical review:** Dr. Ria Singh Rawat
**Article editing:** Dr. Ria Singh Rawat, Dr. Gautam Gokul
**Final approval:** Dr. Gautam Gokul, Dr. Ria Singh Rawat

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