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Authors

Chow, Erica
Clement, Stephen
Garg, Rajesh

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Euglycemic diabetic ketoacidosis in the era of SGLT-2 inhibitors

Erica Chow,¹ Stephen Clement,² Rajesh Garg ¹

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ABSTRACT

Euglycemic diabetic ketoacidosis (EDKA) is an emerging complication of diabetes associated with an increasing use of sodium-glucose transporter type 2 (SGLT-2) inhibitor drugs. This review highlights the growing incidence of EDKA and its diagnostic challenges due to the absence of hallmark hyperglycemia seen in diabetic ketoacidosis (DKA). The paper presents a classification system for the severity of EDKA, categorizing it into mild, moderate, and severe based on serum pH and bicarbonate levels. Another classification system is proposed to define stages of EDKA based on anion gap and ketones at the time of diagnosis and during the treatment period. A treatment algorithm is proposed to guide clinicians in managing EDKA. This treatment algorithm includes monitoring anion gap and ketones to guide insulin and fluid management, and slower transition to subcutaneous insulin to prevent a relapse. Increased awareness of EDKA is essential for a timely diagnosis because an early diagnosis and treatment can improve clinical outcomes.

INTRODUCTION

Euglycemic diabetic ketoacidosis (EDKA) is an acute complication of diabetes that has garnered recent attention due to the growing use of sodium-glucose transporter type 2 (SGLT-2) inhibitor medications. Five SGLT-2 inhibitor drugs (canagliflozin, dapagliflozin, ertugliflozin, empagliflozin, and bexagliflozin) are currently food and drug administration (FDA)-approved in the USA. These drugs are highly effective in achieving target hemoglobin A1c (HbA1c) levels while improving other cardiovascular risk factors in people with type 2 diabetes mellitus (T2DM).¹ They are also useful in improving cardiovascular and renal outcomes in people with T2DM and therefore, preferred in people who have existing cardiac or renal disease.² Canagliflozin was the first to be approved in 2013. Shortly after its approval, reports emerged in 2015 regarding SGLT-2 inhibitor-related cases of diabetic ketoacidosis (DKA).^{3–5} Since then, with the rising use of SGLT-2 inhibitors, there has been increasing recognition of EDKA as more cases are reported.⁶ In this review, we discuss the epidemiology, pathophysiology, and diagnosis, and provide a treatment algorithm to guide clinicians in managing EDKA.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Euglycemic diabetic ketoacidosis (EDKA) is a form of diabetic ketoacidosis known since the early 1970s.
- ⇒ The incidence of EDKA is increasing with increasing use of sodium-glucose transporter type 2 (SGLT-2) inhibitor drugs.

WHAT THIS STUDY ADDS

- ⇒ This review describes the difficulty in diagnosing EDKA when a patient presents to the emergency department.
- ⇒ The review suggests stages of EDKA at presentation and during the treatment period.
- ⇒ The review suggests an algorithm for treatment of EDKA and cautions against premature stopping of insulin infusion due to the high risk of relapse into DKA in the presence of SGLT-2 inhibitors.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ This review will draw attention to an increasing common clinical problem.
- ⇒ The review offers guidelines for diagnosis, grading, and treatment of EDKA. Thus, it will improve clinical care of patients presenting with EDKA.

DEFINITION OF EDKA

DKA is a well-known and life-threatening complication for both type 1 diabetes mellitus (T1DM) and T2DM. It is more common in patients with T1DM with a prevalence ranging from 4.6 to 8.0 per 1000 patient-years⁷ with a mortality rate of 0.65% to 3.3%.⁸ To make a diagnosis of DKA a triad of hyperglycemia above 250 mg/dL, ketonemia, and metabolic acidosis with elevated anion gap is required. EDKA is like DKA but lacks the classic hyperglycemia component. In EDKA, blood glucose (BG) is generally <200 mg/dL, although in some reports a cut-off of 300 mg/dL has been used to define EDKA. We prefer to use a BG threshold of <200 mg/dL, ketonemia (serum β -hydroxybutyrate ≥ 3.0 mmol/L), and at least one of the following criteria to define EDKA:

1. Arterial pH ≤ 7.3
2. Serum bicarbonate ≤ 18 meq/L
3. Anion gap >10 .



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¹Division of Endocrinology, Harbor-UCLA Medical Center, Torrance, California, USA

²Division of Endocrinology, Inova Fairfax Hospital, Falls Church, Virginia, USA

Correspondence to

Dr Rajesh Garg;
rajesh.garg@lundquist.org

EDKA can be further classified as mild with a pH range of 7.25–7.3 and/or serum bicarbonate 15–18 meq/L, moderate with a pH 7.00–7.24 and/or serum bicarbonate 10–15 meq/L, or severe with a pH<7.0 and/or serum bicarbonate <10 meq/L.

EPIDEMIOLOGY

EDKA was first described in 1973 by Munro as a rare occurrence in patients with insulin-dependent diabetes. Of the 211 episodes of DKA in this report, 37 could be considered euglycemic with BG levels <300 mg/dL.⁹ In later years, reports indicated that approximately 2.6%–3.2% cases of DKA presented with euglycemia.^{10 11} However, there is evidence of a changing trend from these early reports of EDKA as the use of SGLT-2 inhibitors increases.

SGLT-2 inhibitors have grown in popularity with a consistent rise in prescriptions from 2015 to 2020.^{12 13} The empagliflozin - remove excess glucose (EMPA-REG) trial of 2015 demonstrated the cardiovascular and renal benefits of SGLT-2 inhibitors, further expanding the clinical application of this class and promoting an increase in prescriptions.¹⁴ Between 2015 to 2020, 63.2 million prescriptions for SGLT-2 inhibitors were dispensed, with annual prescriptions doubling over the 6 years.¹⁵ Another study reported a 114.6% increase in prescription rates between 2016 and 2021.¹⁶ This increase in SGLT-2 inhibitor use could be partially attributed to cardiologist interest after the EMPA-REG results. The EMPA-REG Trial indicated cardiovascular benefit in heart failure with empagliflozin; subsequently, there has been a steady increase in the number of empagliflozin prescriptions (51.7% increase), while canagliflozin initiation trended down (75.1% decrease).¹⁷ Cardiologists showed a 12-fold increase in SGLT-2 inhibitor prescription rates after the EMPA-REG Trial was published.¹⁵ Further expounding the potential benefits of this class, the dapagliflozin in chronic kidney disease (DAPA-CK) study of 2020 indicated that patients with chronic kidney disease on dapagliflozin had decreased progression of their kidney disease and decreased renal, cardiovascular, and all-cause mortality.¹⁸ Considering the multivariate benefits for cardiovascular and renal disease, we anticipate that SGLT-2 inhibitors will continue to rise in popularity.

After 20 cases of DKA associated with SGLT-2 inhibitor use were reported using the FDA Adverse Event Reporting System database, a statement was issued in 2015 warning about increased risk of DKA in patients with T1DM. Within 6 weeks, Health Canada and European Medicines Agency also issued statements.^{3 4} SGLT-2 inhibitors remain unapproved for use in the T1DM demographic¹⁹ and US product labels for SGLT-2 inhibitors depict warnings of the potential for DKA in T2DM, which may include EDKA. Numerous studies have corroborated this association in large-scale clinical trials.^{20–26} For instance, in the Empagliflozin as Adjunctive to Insulin Therapy Trial, the DKA rate in patients with T1DM was 4.3% and 3.3% with empagliflozin 25 mg and 10 mg groups, respectively,

compared with 1.2% in the placebo group.²⁷ DKA associated with SGLT-2 inhibitor use occurs at an incidence of 0.5 per 1000 T2DM patient-years and accounts for about a third of all DKA cases.²⁸

Despite good data on the incidence of DKA, there are relatively few studies that specifically describe events of EDKA in association with SGLT-2 inhibitors. An analysis of the FDA's adverse reporting system revealed a sevenfold increased risk of DKA in the setting of SGLT-2 inhibitor use, of which approximately two-thirds of the reported DKA cases fit the criteria for EDKA.²⁹ In 2018, a review of 105 cases of SGLT-2 inhibitor-associated DKA events revealed average BG levels of 294±188 mg/dL; of these cases, 35.2% qualify as EDKA with a BG threshold of <200 mg/dL.³⁰ Other studies support an association between the use of SGLT-2 inhibitor medications and EDKA^{10 24 31–35} regardless of the duration of exposure.^{25 29 30 36–38} Duration of SGLT-2 inhibitor use before EDKA onset was widely variable with a range of 0.3–420 days.³⁰

Morbidity/mortality

Typical DKA has a mortality rate of 0.65%–3.3%.⁸ Given the diagnostic dilemma of normoglycemia or lower-than-expected BG levels, EDKA portends worse outcomes compared with classic DKA.^{31 39} Most available data on mortality and morbidity of EDKA relates to the condition occurring in pregnant women. Maternal EDKA can increase the rate of fetal demise (up to 9%) and increases maternal mortality.^{40 41} Maternal complications of EDKA also include eclampsia, pre-eclampsia, adult respiratory distress syndrome, acute kidney injury, coma, and death, while fetal complications include malformations, preterm labor, arrhythmias, respiratory distress, hyperbilirubinemia, hypoglycemia, neurologic disorders, and intra-uterine demise.^{42 43} Fortunately, the incidence of EDKA/DKA in diabetic gestations and its associated mortality has significantly declined in more recent years with increased understanding and improved prenatal management.⁴⁴ There are no available data on the mortality or morbidity associated with SGLT-2 inhibitor-induced EDKA.

PATHOPHYSIOLOGY

The mechanism of DKA is well characterized as a clinical state of relative or absolute insulin deficiency and an excessive counter-regulatory hormone response including glucagon, growth hormone, catecholamines, and corticosteroids.⁷ Conversely, our understanding of the mechanisms that contribute to EDKA is more limited. An early theory suggested that EDKA may be attributed to a low renal threshold for glucosuria in the presence of an increased rate of gluconeogenesis and free fatty acid metabolism.⁴⁵ Recent studies have expanded on this idea. SGLT-2 inhibitors increase renal clearance of glucose by inhibiting reabsorption at the SGLT-2 transporters in the renal proximal tubular epithelium. Hepatic gluconeogenesis

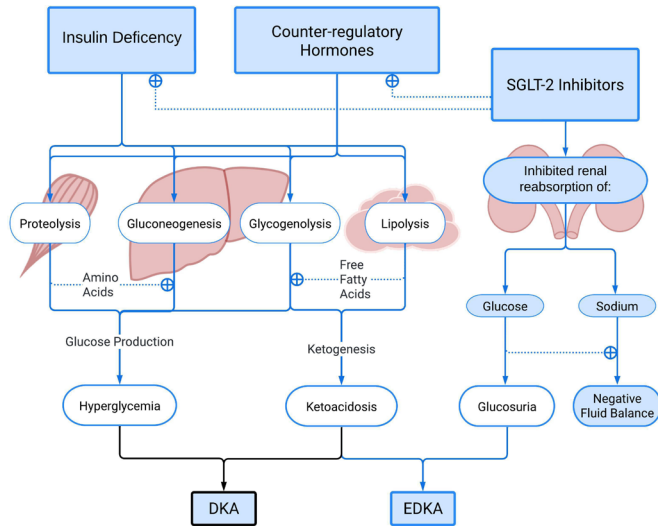


Figure 1 Pathophysiological mechanisms leading to EDKA. EDKA, euglycemic diabetic ketoacidosis; DKA, diabetic ketoacidosis; SGLT-2, sodium-glucose transporter type 2.

is increased at lower insulin dosing with augmentation of urinary glucose losses with SGLT-2 inhibitors²⁵ (figure 1).

Through unclear mechanisms, glucagon levels are elevated in the setting of SGLT-2 inhibitor use.⁴⁶ Upregulated glucagon activity favors ketogenesis.⁴⁷ SGLT-2 inhibitors promote a negative fluid and sodium balance. This exacerbates the hypovolemic state of DKA, leading to elevated cortisol, epinephrine, and glucagon levels, which in turn further enhance insulin resistance, ketogenesis, and lipolysis.^{25 48} A recent study has shown an increase in norepinephrine turnover in response to SGLT-2 inhibitor use that can increase hepatic glucose production independent of changes in insulin and glucagon.⁴⁹

Risk factors

Various risk factors associated with EDKA are described in the literature, with significant overlap between DKA and EDKA triggers. A common theme with cited risk factors for EDKA is that they influence an individual's metabolism towards a state of relative or absolute starvation.^{9 34} Cases of EDKA have been reported in association with anhedonia and anorexia with severe depression³³ and in a patient with Prader-Willi syndrome who was on a low-carbohydrate diet and on ipragliflozin.⁵⁰ Further examples of EDKA triggers include infection/sepsis,^{51 52} exertion, physical stress, decreased caloric intake, cocaine intoxication,⁵³ trauma, dehydration, persistent vomiting, insulin dose reduction/omission, anorexia, gastroparesis,⁵⁴ insulin pump failure,³² acute pancreatitis,⁵⁵ bariatric surgery,^{56–58} prolonged fasting, ketogenic diet, alcohol use disorder, glycogen storage disease, and chronic liver disease.^{11 59–61} Patients with low to normal body mass index on SGLT-2 inhibitor are particularly vulnerable to EDKA,²⁵ as are patients with T1DM when using SGLT-2 inhibitors.²⁵ Some cases noted DKA events in patients with presumed T2DM who were later found to have late autoimmune diabetes instead of T2DM.³⁰ An

association with nausea was also noted, although this may also be a symptom of the EDKA rather than the inciting factor.²⁵

Pregnant women are at a unique risk of developing both DKA and EDKA.^{51 62–64} Pregnancy can be considered a state of accelerated starvation,^{64 65} leading to decreased insulin sensitivity, with subsequent increased lipolysis and ketogenesis.⁵¹ This risk applies to patients with T1DM and T2DM, as well as gestational diabetes.⁴³

Finally, the same mechanisms that can cause metabolic acidosis precipitating DKA can also contribute to EDKA. These mechanisms include lactic acidosis, salicylate overdose, and renal tubular acidosis.⁷⁹ Acute alcohol intoxication can cause an anion gap acidosis, making individuals prone to developing EDKA. Alternatively, chronic alcohol use disorder can lead to dependence on alcohol for calories and create a state of chronic carbohydrate deficiency.^{10 31}

PRESENTATION

EDKA and DKA have significant overlaps in their clinical features. Symptoms of EDKA include nausea, vomiting, malaise, fatigue, anorexia, shortness of breath, tachycardia, and abdominal pain.^{7 25 66} However, the onset of symptoms in EDKA may be more gradual than in DKA.⁵² One notable difference is that due to the absence of pronounced hyperglycemia, patients may not experience the characteristic osmotic symptoms of polyuria, polydipsia, or severe mental status changes. This masking of polyuria and polydipsia is more pronounced in individuals taking SGLT-2 inhibitors due to renal excretion of glucose.³⁹ The renal clearance of glucose (specifically, the ratio of glucosuria to BG levels) is approximately twice as high in EDKA as compared with DKA.⁶⁷

Since EDKA lacks the marked elevation of BG levels anticipated in DKA, clinicians face a diagnostic dilemma. Patients and clinicians may be misled by relatively normal or only mildly elevated point-of-care glucose testing²⁵ and prematurely rule out a metabolic cause for their symptoms. The lower-than-anticipated hyperglycemia can confound the clinical picture and delay the time to diagnosis and treatment, leading to worse outcomes for patients with EDKA.^{31 39} A high clinical suspicion is needed for an accurate diagnosis and timely management.³²

MANAGEMENT

Diagnosis

A thorough history must be obtained, and assessment of medications is essential, including off-label and surreptitious use. History should elicit ingestion of substances that may predispose to metabolic acidosis, such as alcohol. Presentations of alcohol-associated ketoacidosis (AKA) may have significant overlap with DKA and EDKA.⁶⁸ Assessment of serum ketones may be revealing, as AKA exhibits a higher ratio of beta-hydroxybutyrate to acetoacetate as compared with DKA (19:1 AKA vs 11:1 DKA).⁶⁹

Table 1 Stages of EDKA caused by exposure to SGLT-2 inhibitors

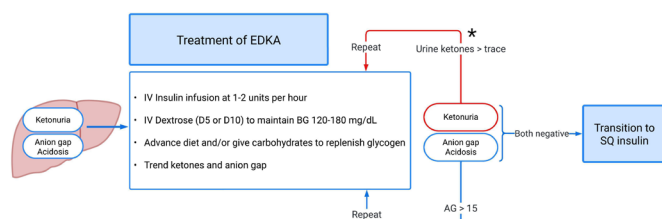
Stage 0	Stage 1	Stage 2	Stage 3
Ketones negative AG<15 Glycosuria	Ketones in low quantity or negative AG<15 Glycosuria	Ketones in moderate or large quantity AG<15 Glycosuria	Ketones in moderate or large quantity AG>15 Glycosuria

AG, anion gap; EDKA, euglycemic diabetic ketoacidosis; SGLT-2, sodium-glucose transporter type 2.

A metabolic panel and serum ketones should be obtained early in the presentation to evaluate for acidosis and ketonemia. Anion gap acidosis in the absence of elevated ketones should prompt further investigation for other causes including sepsis, lactic acidosis, renal failure, ingestion of alcohol, methanol, or polyethylene glycol, and overdose with salicylates and tricyclic acids. As EDKA is a diagnosis of exclusion, other causes of acute anion gap acidosis must be excluded.³¹ In patients with underlying diabetes, suspicion of one or more of these diagnoses should not preclude the possibility of EDKA, as these events may precipitate an EDKA episode, particularly in patients taking SGLT-2 inhibitors. The authors propose a staging system for both diagnosis and for following the progress during treatment of EDKA (table 1).

Treatment

Treatment for EDKA parallels that of DKA except that the risk of relapse into DKA is high in the setting of SGLT-2 inhibitor use (figure 2). Insulin should be delivered at a fixed rate of intravenous infusion until the anion gap corrects and the patient can transition to oral intake. For patients with insulin resistance (ie, body mass index >35 kg/m²), insulin infusion at a fixed rate of 2–3 units/hour is often necessary to correct the acidosis. Dextrose infusion, preferably 10% dextrose water (D10W) is typically necessary in EDKA to prevent hypoglycemia (author experience). DKA is considered resolved when the patient can eat, pH is >7.3 units, bicarbonate is >15.0 mmol/L, and serum ketones are <0.6 mmol/L,⁷ and we recommend the same criteria for resolution of EDKA.

**Figure 2** Proposed treatment algorithm for EDKA.

*Especially important for SGLT-2 inhibitor-related EDKA. BG, blood glucose; EDKA, euglycemic diabetic ketoacidosis; IV, intravenous; SQ, subcutaneous; SGLT-2, sodium-glucose transporter type 2.

Subcutaneous basal insulin should be initiated 2–3 hours before stopping the intravenous insulin infusion. The dose of basal insulin can be based on the patient's body weight (ie, 0.3 units per kilogram per day in both T1DM and T2DM) or based on the rate of intravenous insulin required in the last 6–8 hours before switching to subcutaneous insulin. If the two calculations are discrepant, we suggest the clinician use their best judgment or split the difference between the two calculations. Prandial insulin should be added when the patient starts eating, with the dose calculated as 0.1 units/kg for each meal (for both T1DM and T2DM). Doses of basal and prandial insulin will be adjusted depending on BG levels in subsequent hours and days.

SGLT-2 inhibitors should be paused in the acute setting. Patients may need longer treatment for DKA in the setting of SGLT-inhibitor use. The chances of relapsing back into DKA are high if the insulin drip is stopped prematurely or the dose of basal insulin is inadequate. Therefore, the patient should be closely monitored for an additional 24 hours after the DKA has resolved. Restarting a patient's SGLT-2 inhibitor in the immediate period following EDKA was associated with recurrent DKA or symptomatic ketosis.²⁵ Restarting the medication after the resolution of EDKA should be a personalized, shared decision with the patient and physician to determine underlying triggers that may have contributed, mitigate these as appropriate, and address the possibility of recurrence. In a preoperative period, stopping the SGLT-2 inhibitor 24–48 hours before surgery did not have a significant effect. Optimal methods for preventing postoperative EDKA remain uncertain and deserve further attention.²⁵ At this time, clinicians should consider pausing SGLT-2 inhibitor 3–4 days before surgery, and insulin therapy should be personalized and adjusted accordingly.⁷⁰

Patient education

Prevention of EDKA in patients taking SGLT-2 inhibitors involves patient education about the mechanisms and symptoms of DKA and EDKA, and a thorough review of the risk factors that can predispose to these dangerous conditions. This should also include a discussion on the use of 'sick day rules'.^{24 67} Patients on SGLT-2 inhibitors should be informed that if they start feeling unwell, including nausea and/or vomiting, they should check their BG and consider using a urinary glucose and ketone strip. Patients should be educated that a normal finger-stick glucose test or continuous glucose monitor readings at home do not preclude the possibility of EDKA. Further evaluation by a medical provider should not be dissuaded by the absence of hyperglycemia on a home BG test. Fluids and carbohydrates should be consumed along with supplemental boluses of rapid-acting insulin in the time between symptoms and presentation for a medical evaluation.⁶⁷

CONCLUSION

EDKA is a life-threatening and challenging diagnostic dilemma that is becoming more widespread with the growing use of SGLT-2 inhibitor drugs. This review highlights the need for greater awareness of EDKA among the medical community. We share our approach to diagnosing and treating EDKA to help guide clinicians. Patient education is of particular importance and should be discussed prior to initiating an SGLT-2 inhibitor. Healthcare professionals must remain vigilant and educate patients on the risks and warning signs of EDKA to reduce instances of missed diagnosis and improve overall patient outcomes.

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ORCID iD

Rajesh Garg <http://orcid.org/0000-0002-7779-1619>

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