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# PERIOPERATIVE DIABETIC KETOACIDOSIS ASSOCIATED WITH SODIUM-GLUCOSE CO-TRANSPORTER-2 INHIBITORS : A SYSTEMATIC REVIEW

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## Abstract

*DKA or diabetic ketoacidosis is an emergency condition caused by hyperglycemia in which excessive acid is produced in the blood. Patients with type 1 and type 2 diabetes who undergo surgery, have an infection, or are under extreme stress can also develop DKA. The body generates the hormone adrenaline to combat infection and stress, but this can have a negative effect on blood glucose levels (adrenaline is counterinsulin). This can worsen if the patient refuses to take diabetes medication or inject insulin during stressful or infectious situations. The fundamental components of the pathophysiological mechanisms at play in diabetic ketoacidosis (DKA) include shifts in hormone levels and the ensuing inflammatory response. Alterations in the concentration of hormones lead to shifts in the production and consumption of glucose, as well as an increase in lipolysis and the formation of ketone bodies. Canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin are agents approved by the Food and Drug Administration (FDA) for the treatment of type 2 diabetes mellitus (DM) in adults. Acting on proteins, the four agents are SGLT2 inhibitor class agents. SGLT-2 is expressed in the kidney's proximal tubule. This may result in a decrease in filtered glucose reabsorption, a decrease in the renal threshold for glucose (RTG), and an increase in glucose excretion via urine. Diabetes patients treated with sodium–glucose transport protein 2 (SGLT2) inhibitors have also been reported to experience DKA. The results of a study indicate that DKA is uncommon among T2DM patients treated with SGLT2 inhibitors.*

**Keyword:** *Diabetic ketoacidosis; Diabetes mellitus; Sodium-glucose co-transporter-2 inhibitors; Surgery*

## INTRODUCTION

Diabetes Mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various glands, especially the eyes, kidneys, nerves, heart, and blood vessels.[1] About 10.2 million people in the United States have DM. Meanwhile, in Indonesia the prevalence of DM is 1.5-2.3% of the population aged> 15 years, even in the Manado area the prevalence of DM is 6.1%. The incidence of Type 2 DM in women is higher than men.[2–4]

DKA, also known as diabetic ketoacidosis, is a life-threatening illness caused by hyperglycemia in which a significant amount of acid is produced in the blood.[5–7] Patients with type 1 and type 2 diabetes can also have DKA, which occurs when the body creates the hormone adrenaline to deal with illness and stress, but this can have a detrimental consequence since it causes a spike in blood glucose (adrenaline is counterinsulin). DKA can also occur after surgery, an infection, or severe stress. During times of stress or infection, the patient's resistance to taking their diabetic medicine or injecting insulin may cause this problem to become even more severe.[8]

Errors or omissions in the use of insulin can cause DKA. Insulin medication given in a dual-dose regimen is the main cause. However, data from the UK National Pediatric Diabetes Audit show that insulin pump use is also associated with an increased risk of DKA in those aged <18 years. DKA has also been reported in people with diabetes mellitus who were treated with sodium–glucose transport protein 2 (SGLT2) inhibitors. Results from randomized controlled trials have shown that DKA rarely occurs in patients with T2DM who are treated with SGLT2 inhibitors (incidence 0.16–0.76 events per 1000 patient-years).[9,10]

Canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin are all examples of medications that have been given the go-ahead by the Food and Drug Administration (FDA) to be used in the treatment of diabetes mellitus type 2 in adult patients. Ertugliflozin is another medication in this class. Because of their action on proteins, these four medicines belong to the SGLT2 inhibitor class. The proximal tubule of the kidney is the location where SGLT-2 is expressed. This can result in a reduction in the amount of filtered glucose that is reabsorbable, a reduction in the renal threshold for glucose (RTG), and an increase in the amount of glucose that is excreted in the urine.[11]

However, some RCTs have reported a higher risk of ketosis associated with SGLT2 inhibitors in adults with T1DM (5-12%) and an incidence of DKA of ~3-5% in those with T1DM treated with SGLT inhibitors. The incidence of DKA in those receiving placebo in RCTs of people with T1DM was 0-1.9%, and DKA occurred despite the use of measures designed to minimize the risk of ketosis.[9,10] The aim of this research is to assess the perioperative diabetic ketoacidosis associated with sodium-glucose co-transporter-2 inhibitors.

## METHODS

By checking the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 criteria, the author of this study made certain that it was up to standard and satisfied all of the requirements. This is done in order to guarantee that the findings of the investigation are accurate. What this study found perioperative diabetic ketoacidosis associated with sodium-glucose co-transporter-2 inhibitors. The best way to accomplish this is to review the work that has been done previously on the topic. The purpose of this post is to demonstrate why the issues that have been brought up are so important.

Before participating in the investigation, researchers had to demonstrate that they met the following criteria: 1) To be considered for publication, the paper must be written in English and its primary concentration must be on assoction of perioperative diabetic ketoacidosis associated with sodium-glucose co-transporter-2 inhibitors. 2) This evaluation considers works published after 2018, but prior to the evaluation period. Research that cannot be published includes editorials, applications without a DOI, previously published review articles, and entries that are nearly identical to previously published journal papers.

We used "perioperative diabetic ketoacidosis" and "sodium-glucose co-transporter-2 inhibitors" as keywords.The search for studies to be included in the systematic review was carried out from May, 24th 2023 using the PubMed and SagePub databases by inputting the words: *("perioperative"[All Fields] OR "perioperatively"[All Fields]) AND ("diabetic ketoacidosis"[MeSH Terms] OR ("diabetic"[All Fields] AND "ketoacidosis"[All Fields]) OR "diabetic ketoacidosis"[All Fields]) AND "sodium-glucose"[All Fields] AND "co-transporter-2"[All Fields] AND ("antagonists and inhibitors"[MeSH Subheading] OR ("antagonists"[All Fields] AND "inhibitors"[All Fields]) OR "antagonists and inhibitors"[All Fields] OR "inhibitors"[All Fields] OR "inhibitor"[All Fields] OR "inhibitor s"[All Fields])* used in searching the literature.

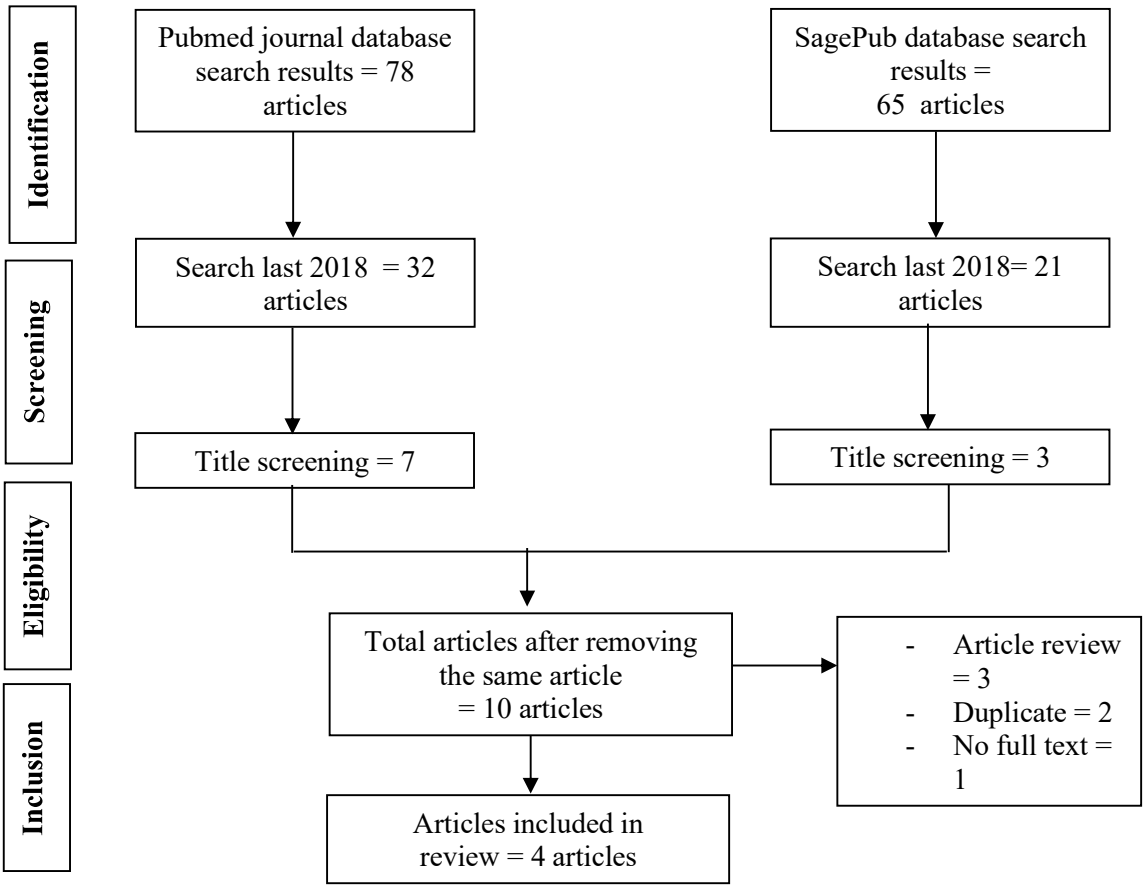


**Figure 1. Article search flowchart**

The eligibility of each study was determined based on its abstract and title. Afterwards, they consulted historical archives. Numerous investigations employing the same methodology led to this result. Required are unpublished English contributions. The systematic review only included studies that met the inclusion criteria. This narrows the results of the search. Insufficient research findings are not investigated. The analysis will then follow. The paper disclosed the participants' identities, authors, publication dates, location, study activities, and parameters. Endnote eliminated duplicate results from the search results list. The titles and abstracts of relevant articles were examined by two reviewers.

Initially, their entire papers were reviewed for eligibility and data collection. GWG and other health issues have been the subject of reviews, animal studies, conference papers, and studies. During their deliberation, the judges came to an agreement. Before deciding which papers to analyze in greater depth, each author reviewed the studies listed in the titles and abstracts of each publication. Then, we will investigate all papers that meet the inclusion criteria of the review and are worthy of inclusion. Then, we'll select which articles to include in the review based on what we've learned. Both the papers to be reviewed and those to be investigated are selected in this manner.

**RESULT**

Study by Mehta, et al (2022)[12] with the majority (79.1%) being non-emergent patients. 625 (47.8%) of 1307 patients were prescribed empagliflozin, 447 (34.2%) were prescribed canagliflozin, 214 (16.4%) were prescribed dapagliflozin, and 21 (1.6%) were prescribed ertugliflozin. There were a total of 8 cases of eDKA in 8 patients, of which 5 had undergone emergency surgery and 3 had undergone non-emergency procedures. In the three non-emergent cases, only one patient was counseled to discontinue SGLT2i three days prior to the procedure. Over a 6-year period, the incidence of eDKA in perioperative patients who were prescribed an SGLT2i was 0.17 percent for non-emergency procedures and 1.11 percent for emergency procedures.

Chaudhry, et al (2022)[13] counducted a case series with 4 patients. SGLT2i were held for a period ranging from one to five days before to surgery, with the amount of time that had passed since the patient's last dose being 54, 79, 80, and 151 hours respectively. The patients who need surgery did so because it was either semiurgent or elective. Within the first twenty-four hours following surgery, the condition of euglycemic DKA was identified in three patients. The fourth patient had euglycemic DKA on the third postoperative day, which occurred in the context of substantial hypovolemia. This patient also demonstrated probable symptoms of delayed SGLT2i action seven days after the patient's most recent dose.

**Table 1. The litelature include in this study**

| Author | Origin | Method | Sample Size | Result |
|---|---|---|---|---|
| Mehta, 2022[12] | United State of America (USA) | Cross sectional | 2,183 procedures conducted on 1,307 patients | Patients who were undergoing non-emergent procedures had a low risk of developing euglycemic DKA, most likely as a result of preoperative advice to stop taking their SGLT2i medication three days before the procedure. Patients undergoing emergency surgery had a higher risk of developing euglycemic DKA if the SGLT2i couldn't be halted prophylactically. This increased the risk of hypoglycemia. |
| Chaudhry, 2022[13] | Canada | Retrospective, single-centre case series | 4 patients | The period of action of SGLT2i is vary, and the risk for developing DKA is complex. The SGLT2 inhibitor should be withheld at least three days before an elective major surgery, and possibly for longer periods of time in high-risk individuals. All patients who have recently been exposed to SGLT2i should be monitored carefully for the development of perioperative DKA. |
| Auerbach, 2023[14] | United State of America (USA) | Cross sectional | 1,654 patients undergoing cardiac surgery | It was found that postoperative eDKA was associated with prolonged CVICU LOS and occurred in 15% of patients who had been taking an SGLT2i before to heart surgery. Future investigations into SGLT2i treatment perioperatively are necessary. |
| Lui, 2023[15] | China – Hong Kong | Cross sectional | 147,115 subjects | In patients with type 2 diabetes, preoperative usage of SGLT2i was related with an increased risk of surgical DKA. It is possible for clinicians to improve patients' results by prescribing the appropriate amount of SGLT2i while keeping an eye out for high-risk characteristics. It is possible that implementing automatic pop-up notifications inside electronic health records can lower the incidence of postoperative DKA related with SGLT2i. |

Other study showed SGLT2i prevalence and eDKA frequency were assessed in cardiac surgery patients admitted within 24 hours from February 2, 2019 to May 26, 2022. Wilcoxon rank sum and chi-square testing compared results. 53 (3.2%) of 1,654 cardiac surgery patients received an SGLT2i before surgery; 15.1% had eDKA. The authors found no differences between patients with and without SGLT2i use in hospital LOS (median [IQR]: 4.5 [3.5-6.3] v 4.4 [3.4-5.6] days, p = 0.46) or CVICU LOS (median [IQR]: 1.2 [1.0-2.2] v 1.1 [1.0-1.9] days, p = 0.22), 30-day mortality (1.9% v 0.7%, p = 0.31), or sternal infections (0.0% v 0.3%, p = 0. SGLT2i patients with eDKA exhibited longer CVICU LOS (2.2 [1.5-2.9] v 1.2 [0.9-2.0], p = 0.042) but equivalent hospital LOS (5.1 [4.0-5.8] v 4.4 [3.4-6.3], p = 0.76).[14]

Lui, et al (2023) study showed preoperative SGLT2i exposure increased postoperative DKA risk (6.40/1,000 person-years; IRR 6.33, 95% CI 5.57-7.18; p < 0.001). Emergency surgery, preoperative HbA1c of 8%, and insulin use were risk factors for SGLT2i-associated postoperative DKA. SGLT2i users who developed postoperative DKA had worse outcomes (p < 0.05) than those who did not, but they had better outcomes than non-users. An automatic electronic health record pop-up alert on perioperative precaution for SGLT2i reduced postoperative DKA risk (from IRR 4.06 [95% CI 3.41-4.83] to 2.97 [95% CI 2.41-3.65]; p for interaction = 0.020).[15]

## DISCUSSION

DKA is an emergency situation due to hyperglycemia where a lot of acid is formed in the blood. This state is sometimes called “accelerated fasting” and is the most serious metabolic disturbance in insulin-dependent diabetes. This happens because muscle cells are no longer able to form energy so that in this emergency the body will break down fat and form toxic acids in the blood circulation called ketones.[8] Diabetic ketoacidosis can occur in patients experiencing absolute or relative insulin deficiency or during acute illness which is associated with increased counter-regulatory hormones cortisol, growth hormone, glucagon, and catecholamines.

The fundamental components of the pathophysiological mechanisms at play in diabetic ketoacidosis (DKA) include shifts in hormone levels and the ensuing inflammatory response. Alterations in the concentration of hormones lead to shifts in the production and consumption of glucose, as well as an increase in lipolysis and the formation of ketone bodies.

Hyperglycemia can be caused by co-morbidities, which can also promote counterregulatory hormone production, and diabetic ketoacidosis can be triggered by pro-inflammatory circumstances brought on by infections.[5,16]

Canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin are drugs that have been approved by the Food and Drug Administration (FDA) as agents for treating adult patients with type 2 diabetes mellitus (DM). The four agents are SGLT2 inhibitor class agents by acting on proteins. SGLT-2 is expressed in the proximal tubule of the kidney. This can cause a decrease in filtered glucose reabsorption, lower the renal threshold for glucose (RTG), and increase glucose excretion in the urine.[11]

Canagliflozin was the first SGLT-2 inhibitor to receive FDA approval on March 29, 2013. This agent is indicated in adult type 2 DM patients to improve blood glucose control in addition to using diet and exercise therapy. This agent is also indicated to reduce the risk of cardiovascular side effects in type 2 DM subjects with cardiovascular disease and minimize the risk of end stage renal disease (ESRD), cardiovascular mortality, hospitalization for heart failure, and increased serum creatinine in type 2 DM patients with diabetic nephropathy. as well as albuminuria.[11,17]

Patients with T2DM who are treated with SGLT2 inhibitors infrequently develop DKA, according to randomized controlled trials (incidence 0.16–0.76 events per 1000 patient-years). Nonetheless, some randomized controlled trials (RCTs) have reported a higher risk of ketosis associated with SGLT2 inhibitors in adults with T1DM (5-12%) and an incidence of DKA of 3-5% in T1DM patients treated with SGLT inhibitors. In RCTs of persons with T1DM, the incidence of DKA in those receiving placebo ranged from 0% to 1.9%, despite the use of measures designed to minimize the risk of ketosis.[9,10]

Surgical SGLT2i-associated ketoacidosis pathogenesis is complex. A cells need SGLT2 to sense glucose and regulate glucagon secretion. Glycosuria from proximal renal tubule SGLT2 inhibition lowers plasma glucose. This decreases pancreatic beta cell insulin synthesis, which stimulates alpha cells and raises plasma glucagon. SGLT2i independently stimulates alpha cells, increasing plasma glucagon levels. This insulin:glucagon ratio change increases lipolysis, hepatic fatty acid oxidation, and liver ketogenesis. Glycogenolysis and gluconeogenesis increase hepatic glucose production. Surgery and illness boost adrenaline and cortisol, which enhance insulin resistance and protein catabolism.[18,19]

Liver amino acid absorption and gluconeogenesis boost glucose production. Endogenous hepatic glucose production, renal glucose clearance, and diet carbohydrate determine euglycaemia or hyperglycaemia in DKA. SGLT2i enhance ketone body and decrease renal salt reabsorption. Indirect reservoir enlargement causes ketoacidosis without ketonuria. Urine ketones cannot detect SGLT2i-associated DKA. Renal glucose excretion and ketone body production may keep CBG normal or slightly elevated. glycosuria, not. Others may have measured but not reported. Urinary glucose is inaccurate in this patient population due to SGLT2i-induced urine glucose losses.[18–20]

## CONCLUSION

The results from this study indicate that DKA occurs frequently in patients with T2DM who are treated with SGLT2 inhibitors

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