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EUGLYCEMIC DIABETIC KETOACIDOSIS ASSOCIATED WITH SGLT2 INHIBITORS IN NON-PERIOPERATIVE SETTINGS: A SYSTEMATIC REVIEW

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ABSTRAK

Inhibitor sodium–glucose cotransporter-2 (SGLT2) memberikan manfaat kardiometabolik, tetapi dapat menyebabkan ketoasidosis diabetik euglikemik (euDKA), yaitu ketoasidosis tanpa hiperglikemia yang bermakna. Penelitian ini bertujuan untuk meninjau kejadian dan karakteristik euDKA terkait inhibitor SGLT2 pada kondisi non-perioperatif. Penelusuran sistematis dilakukan pada PubMed, Cochrane Library, dan ScienceDirect terhadap studi pada pasien dewasa. Delapan studi yang dipublikasikan pada 2019–2024, terdiri atas enam kohort dan dua analisis farmakovigilans, diikutsertakan dan disintesis secara naratif. EuDKA mencakup proporsi bermakna kasus ketoasidosis terkait SGLT2, dengan pencetus utama berupa infeksi, puasa atau penurunan asupan karbohidrat, dehidrasi, dan penghentian insulin. Meskipun kadar glukosa lebih rendah, tingkat keparahan metabolik, kebutuhan perawatan intensif, dan lama rawat inap sebanding dengan ketoasidosis diabetik hiperglikemik, sedangkan mortalitasnya rendah. EuDKA merupakan komplikasi penting terapi SGLT2 yang dapat terlambat terdiagnosis sehingga diperlukan kewaspadaan klinis, evaluasi biokimia dini, dan pencegahan.

ABSTRACT

Euglycemic Diabetic Ketoacidosis Associated With Sglt2 Inhibitors In Non-Perioperative Settings: A Systematic Review. Sodium–glucose cotransporter-2 (SGLT2) inhibitors provide cardiometabolic benefits but may cause euglycemic diabetic ketoacidosis (euDKA), characterized by ketoacidosis without marked hyperglycemia. This study aimed to review the euDKA associated with SGLT2 inhibitors in non-perioperative settings. A systematic search of PubMed, Cochrane Library, and ScienceDirect identified studies involving adults receiving SGLT2 inhibitors. Eight studies published between 2019 and 2024, comprising six cohort studies and two pharmacovigilance analyses, were included and narratively synthesized. EuDKA represented a substantial proportion of SGLT2 inhibitor–associated ketoacidosis cases, with infection, fasting or reduced carbohydrate intake, dehydration, and insulin omission as common triggers. Despite lower glucose levels, metabolic severity, intensive care requirements, and hospital stay were comparable to hyperglycemic diabetic ketoacidosis, while mortality was low. EuDKA is an important complication of SGLT2 inhibitor therapy that may be under-recognized, highlighting the need for clinical awareness, early biochemical evaluation, and preventive strategies.

INTRODUCTION

Sodium–glucose cotransporter-2 (SGLT2) inhibitors have become an integral component of modern cardiometabolic therapy. Initially developed as glucose-lowering agents for type 2 diabetes mellitus (T2DM), these drugs have demonstrated robust cardiovascular and renal protective effects that extend beyond glycemic control.1,2 Large landmark trials have shown significant reductions in cardiovascular mortality, heart failure hospitalizations, and progression of chronic kidney disease among patients treated with empagliflozin and dapagliflozin, leading to their widespread incorporation into international clinical guidelines for the management of diabetes, heart failure, and chronic kidney disease. Consequently, SGLT2 inhibitors are now prescribed to an increasingly diverse and medically complex patient population, often in outpatient and inpatient medical settings.

Despite these substantial benefits, accumulating post-marketing data have revealed rare but clinically important adverse effects associated with SGLT2 inhibitor therapy. Among these, euglycemic diabetic ketoacidosis (euDKA) has emerged as a distinctive and potentially under-recognized complication. Unlike classical diabetic ketoacidosis (DKA), which is typically characterized by severe hyperglycemia, euDKA presents with metabolic acidosis and ketonemia despite normal or only mildly elevated blood glucose concentrations, usually below 250 mg/dL.[3] This atypical biochemical profile challenges traditional diagnostic paradigms and may delay appropriate diagnosis and treatment, particularly in acute care settings where hyperglycemia is often relied upon as a key diagnostic trigger.

The biological mechanisms underlying SGLT2 inhibitor–associated euDKA are complex and multifactorial. By inhibiting renal glucose reabsorption, SGLT2 inhibitors promote persistent glycosuria, leading to reductions in circulating insulin levels and a compensatory increase in glucagon secretion.[4] This altered insulin-to-glucagon ratio shifts metabolic balance toward enhanced lipolysis and hepatic ketogenesis. Additionally, SGLT2 inhibitors may directly stimulate ketone reabsorption in the renal tubules, further increasing circulating ketone levels.[5] In parallel, reduced carbohydrate availability, whether due to fasting, illness-related anorexia, or intentional dietary restriction, amplifies ketone body production. The continued renal excretion of glucose during ketoacidosis effectively masks hyperglycemia, allowing significant ketoacidosis to develop in the absence of marked elevations in plasma glucose.

Regulatory agencies first highlighted the association between SGLT2 inhibitors and diabetic ketoacidosis in 2015, prompting safety communications from both the U.S. Food and Drug Administration and the European Medicines Agency.[6,7] Since then, an expanding body of literature has described cases of euDKA associated with SGLT2 inhibitor use across a variety of clinical scenarios. While perioperative fasting and surgical stress have been well recognized as triggers, emerging evidence suggests that euDKA frequently occurs in non-perioperative settings, including during acute infections, dehydration, starvation, insulin omission, and routine medical hospitalizations.[8] These contexts are particularly relevant given the growing use of SGLT2 inhibitors among patients with multiple comorbidities and fluctuating physiological stressors.

Observational cohort studies and pharmacovigilance analyses have reported that euDKA may represent a substantial proportion of SGLT2 inhibitor–associated DKA cases. Some studies suggest that more than half of DKA episodes occurring in patients receiving SGLT2 inhibitors meet criteria for euglycemia at presentation.[8,9] Although euDKA is often associated with less severe hyperglycemia, its overall clinical severity remains incompletely understood. Several reports have

documented comparable degrees of metabolic acidosis, similar requirements for intensive care, and prolonged hospital stays when compared with hyperglycemic DKA, highlighting that euDKA is not necessarily a benign entity.[9] Moreover, the absence of severe hyperglycemia may lead to delayed diagnosis, increasing the risk of treatment complications such as hypoglycemia during insulin therapy.

Current evidence on SGLT2 inhibitor–associated euDKA is heterogeneous, encompassing spontaneous adverse event reporting systems, population-based cohort studies, and hospital-based retrospective analyses. Pharmacovigilance studies provide valuable insights into safety signals and reporting patterns at a population level but lack detailed biochemical and clinical information.[10] Conversely, hospital-based cohorts offer granular clinical data but are often limited by small sample sizes and retrospective design. Importantly, many published reviews and analyses have focused broadly on DKA or on perioperative contexts, leaving a gap in synthesis that specifically addresses euDKA in non-perioperative clinical settings.

Although SGLT2 inhibitor–associated ketoacidosis remains uncommon in absolute terms, its clinical burden is increasingly relevant because of the rapid expansion of SGLT2 inhibitor indications across diabetes, heart failure, and chronic kidney disease populations. Real-world cohort data suggest that diabetic ketoacidosis occurs in approximately 2 per 1,000 patients initiating SGLT2 inhibitor therapy, while comparative observational studies have reported an approximately two- to three-fold higher relative risk of DKA among SGLT2 inhibitor users compared with users of other glucose-lowering agents such as DPP-4 inhibitors. This distinction between low absolute incidence and increased relative risk is clinically important, as even rare adverse events may translate into a meaningful number of cases when these agents are prescribed to broad and medically complex populations. Moreover, the euglycemic phenotype may further increase clinical burden by delaying recognition, because patients may present with significant ketonemia and metabolic acidosis despite normal or only mildly elevated glucose concentrations.

Recent clinical guidance also reflects growing concern regarding this safety issue. The American Diabetes Association recommends temporary withholding of SGLT2 inhibitors before elective surgery and emphasizes that euglycemic DKA should be considered in at-risk patients, particularly during acute illness or physiological stress. Similarly, kidney disease guidance, including KDIGO-based recommendations, highlights the importance of “sick-day” protocols, such as temporarily discontinuing SGLT2 inhibitors during illness, poor oral intake, dehydration, excessive exercise, or alcohol exposure. However, most safety discussions and previous syntheses have emphasized perioperative or procedure-related euDKA, whereas non-perioperative presentations in routine medical illness, outpatient care, emergency admissions, or hospitalizations remain less systematically characterized. This gap is clinically relevant because infection, starvation, dehydration, and insulin omission are common real-world stressors that may occur outside surgical settings. Therefore, a focused synthesis of observational evidence on SGLT2 inhibitor–associated euDKA in non-perioperative contexts is needed to clarify its occurrence, triggers, clinical severity, and implications for routine practice.

To date, no systematic review has comprehensively integrated observational and trial evidence to characterize the occurrence, precipitating factors, and clinical outcomes of euglycemic diabetic ketoacidosis associated with SGLT2 inhibitors outside the perioperative setting. A focused synthesis of this evidence is essential to improve clinician awareness, support early recognition, and inform risk mitigation strategies in routine medical practice. Therefore, this systematic review aims to summarize the available evidence on SGLT2 inhibitor–associated euDKA in non-perioperative

contexts, with particular emphasis on its frequency, triggering factors, clinical presentation, disease severity, and in-hospital outcomes.

METHODS

Study Design and Reporting Framework

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The review protocol was developed a priori to identify, screen, and synthesize observational and trial evidence examining euglycemic diabetic ketoacidosis associated with SGLT2 inhibitor use in non-perioperative clinical settings. Given the heterogeneity of study designs and outcome reporting, a qualitative synthesis approach was adopted.

Data Sources and Search Strategy

A comprehensive literature search was performed across three electronic databases: PubMed, Cochrane Library, and ScienceDirect. The search strategy was specifically refined to balance sensitivity and specificity and to ensure retrieval of all eligible studies while minimizing irrelevant records.

Database-specific keyword combinations were developed using terms related to SGLT2 inhibitors (including empagliflozin, dapagliflozin, canagliflozin, and ertugliflozin) and euglycemic diabetic ketoacidosis. Broad diabetic ketoacidosis terms without explicit SGLT2 inhibitor context were intentionally avoided to reduce non-relevant retrieval. Searches were conducted without restrictions on publication year. Only studies published in English were considered.

The final search strategies for each database are provided in the Supplementary Materials. Reference lists of included studies were manually screened to identify additional relevant publications.

Eligibility Criteria

Studies were selected based on predefined inclusion and exclusion criteria.

Eligible studies met all of the following criteria:

- Included adult patients (≥18 years) with diabetes mellitus receiving SGLT2 inhibitors
- Reported cases or cohorts of euglycemic diabetic ketoacidosis, or provided sufficient data to identify euDKA among DKA cases
- Were conducted in non-perioperative clinical settings, including outpatient care, emergency departments, medical wards, or intensive care units
- Utilized observational study designs (cohort, case–control, pharmacovigilance analyses) or interventional trial data with relevant outcomes

Studies were excluded if they:

- Focused exclusively on perioperative or surgical settings
- Included only pediatric populations
- Were case reports, narrative reviews, editorials, or conference abstracts without sufficient data
- Did not clearly document SGLT2 inhibitor exposure

Study Selection

All records identified through database searching were imported into a reference management system, and duplicates were removed. Two reviewers independently screened titles and abstracts to assess eligibility. Full-text articles were retrieved for records deemed potentially eligible. Discrepancies at any stage of screening were resolved through discussion and consensus.

The study selection process and reasons for exclusion at each stage are summarized in the PRISMA flow diagram.

All records identified in electronic databases were imported into a reference management system and initially screened by title and abstract. Two reviewers (AA and UF) independently screened the titles and abstracts of all identified records according to the predefined eligibility criteria. Records considered potentially eligible by either reviewer were retained for duplicate checking and full-text assessment. Duplicate records were then identified and removed before full-text review. The same two reviewers independently assessed the remaining full-text articles for final inclusion. Disagreements during title–abstract screening or full-text review were resolved through discussion and consensus with a third reviewer (AI). Inter-rater agreement was not formally quantified; however, all disagreements were documented and resolved by consensus. Reasons for exclusion at the full-text stage were documented and presented in the PRISMA flow diagram.

Data Extraction

Data were extracted independently by two reviewers using a standardized data extraction form. Extracted variables included:

- Study characteristics (author, year, country, study design, setting)
- Population characteristics (sample size, age, sex, diabetes type)
- Details of SGLT2 inhibitor exposure
- Comparator groups, where applicable
- Diagnostic criteria for euglycemic diabetic ketoacidosis
- Reported precipitating factors
- Clinical severity indicators and in-hospital outcomes

Extracted data were cross-checked for accuracy, and disagreements were resolved by consensus. No attempts were made to contact study authors for missing data.

Risk of Bias Assessment

The risk of bias was assessed independently by two reviewers according to the study design. Observational cohort studies were evaluated using the Newcastle–Ottawa Scale (NOS), which assesses three major domains: selection of study groups, comparability of cohorts, and ascertainment of exposure or outcome. Studies with 7–9 stars were considered high quality, studies with 4–6 stars were considered moderate quality, and studies with fewer than 4 stars were considered low quality. Pharmacovigilance studies were assessed using a structured quality framework adapted for spontaneous adverse event reporting analyses, including clarity of case definition, appropriateness of database source, exposure and outcome ascertainment, reporting of disproportionality methods, handling of duplicate reports, and acknowledgment of reporting bias and missing denominator data. Any disagreements in quality assessment were resolved through discussion and consensus. The detailed risk-of-bias assessment for each included study is presented in a separate table.

Data Synthesis

Due to heterogeneity in study design, population characteristics, outcome definitions, and reporting formats, a meta-analysis was not performed. Instead, findings were synthesized narratively, with results summarized according to study type, occurrence of euglycemic diabetic ketoacidosis, precipitating factors, clinical presentation, disease severity, and in-hospital outcomes.

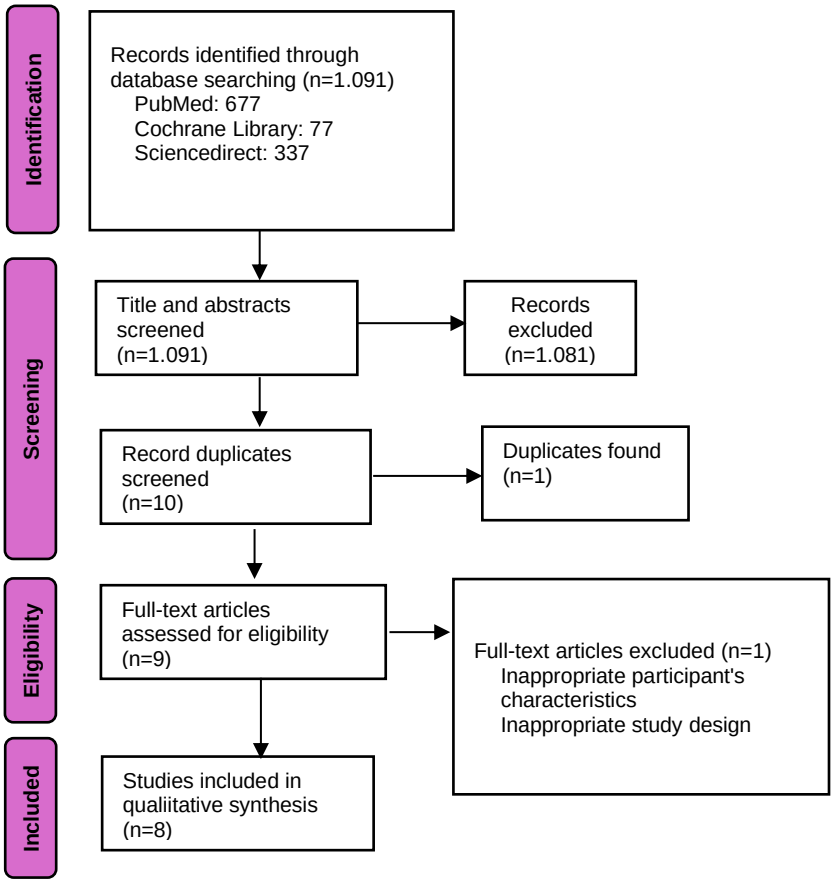

Figure 1. Diagram flow of literature search strategy for this systematic review

RESULTS

Study Selection

The systematic literature search identified 1,091 records from electronic databases, including 677 from PubMed, 77 from the Cochrane Library, and 337 from ScienceDirect. All records underwent title and abstract screening, during which 1,081 records were excluded because they were unrelated to SGLT2 inhibitor–associated euglycemic diabetic ketoacidosis, focused on perioperative or surgical settings, involved non-adult or non-human populations, were non-original articles, or did not provide relevant clinical data. Ten records were then assessed for duplication, and one duplicate record was removed. Nine full-text articles were subsequently assessed for eligibility. Of these, one article was excluded because it did not meet the predefined criteria for participant characteristics and study design. Finally, eight studies were included in the qualitative synthesis. The study selection process is presented in the PRISMA flow diagram.

Characteristics of Included Studies

The eight included studies were published between 2019 and 2024 and consisted of six retrospective observational cohort studies and two pharmacovigilance analyses. The cohort studies were conducted in hospital-based settings, including emergency departments, medical wards, and intensive care units, whereas the pharmacovigilance studies used large spontaneous adverse event reporting databases. The included studies represented diverse geographic regions, including North America, Europe, East Asia, Australia, and the Middle East. Most cohort studies included patients with type 2 diabetes mellitus, although several studies also included mixed or unspecified diabetes populations. Across the included studies, the reported SGLT2 inhibitors included empagliflozin, dapagliflozin, canagliflozin, and ertugliflozin. Comparator groups varied across studies and included patients with hyperglycemic diabetic ketoacidosis, patients not exposed to SGLT2 inhibitors, and patients receiving other glucose-lowering agents such as DPP-4 inhibitors.

Occurrence of Euglycemic Diabetic Ketoacidosis

Across the included studies, euglycemic diabetic ketoacidosis represented a clinically important phenotype of SGLT2 inhibitor–associated diabetic ketoacidosis. In hospital-based cohorts that directly classified DKA cases by glucose level at presentation, euDKA accounted for a substantial proportion of SGLT2 inhibitor–associated DKA cases, with several studies reporting that more than half of DKA events among SGLT2 inhibitor users met euglycemic criteria. In comparative cohorts, patients with euDKA consistently had markedly lower presenting plasma glucose levels than those with hyperglycemic DKA, while still meeting biochemical criteria for ketoacidosis, including metabolic acidosis, ketonemia or ketonuria, and an elevated anion gap.

The two pharmacovigilance studies also demonstrated consistent safety signals linking exposure to SGLT2 inhibitors with euglycemic or atypical DKA presentations. These studies reported disproportionate adverse event signals for DKA or euDKA across multiple SGLT2 inhibitors, supporting the interpretation that the association is likely a class-related safety concern rather than limited to a single drug. However, because pharmacovigilance databases do not provide reliable denominator data, these studies were interpreted as signal-detection evidence rather than direct incidence estimates.

Precipitating Factors and Clinical Presentation

Precipitating factors were reported in most hospital-based cohort studies. The most consistently identified triggers were acute infection, reduced oral intake or starvation, dehydration or volume depletion, and insulin omission or dose reduction. Less frequently reported triggers included alcohol intake, pancreatitis, glucocorticoid exposure, and low-carbohydrate dieting. Infection was commonly observed among hospitalized patients, while reduced carbohydrate intake was frequently reported in the context of acute illness, nausea, vomiting, or intentional dietary restriction. These findings indicate that non-perioperative physiological stressors are central to the development of euDKA among SGLT2 inhibitor users.

The clinical presentation of euDKA was generally nonspecific. Common symptoms included nausea, vomiting, abdominal pain, malaise, weakness, and reduced oral intake. Compared with hyperglycemic DKA, euDKA was consistently characterized by lower glucose levels at presentation, but abnormalities in acid–base status and ketone metabolism remained clinically significant. Several studies have reported that the absence of marked hyperglycemia contributes to diagnostic

uncertainty or delay, emphasizing that normal or mildly elevated glucose levels do not rule out clinically important ketoacidosis in patients receiving SGLT2 inhibitors.

Clinical Severity and In-Hospital Outcomes

Clinical severity indicators varied across the included studies, but several consistent patterns were observed. Although patients with euDKA had lower presenting glucose concentrations than patients with hyperglycemic DKA, the degree of metabolic disturbance was not uniformly mild. Reported pH, bicarbonate, anion gap, and ketone abnormalities indicated clinically significant ketoacidosis. Intensive care unit admission was reported in several cohort studies, with variable rates across institutions. Some studies found comparable ICU utilization between euDKA and hyperglycemic DKA, whereas others reported differences in ICU length of stay or treatment complexity.

Hospital length of stay also varied across studies, generally ranging from a few days to more than one week depending on study population, severity at presentation, and local admission practices. Mortality was consistently low among hospital-based studies, with most cohorts reporting no deaths or very few fatal outcomes. Nevertheless, the requirement for hospitalization, insulin infusion, fluid resuscitation, electrolyte correction, and close biochemical monitoring indicates that euDKA should not be interpreted as a benign variant of DKA solely because glucose levels are not markedly elevated.

Risk of Bias Assessment

The overall risk of bias among the included studies was assessed as low to moderate. Pharmacovigilance studies were inherently limited by under-reporting, lack of standardized biochemical data, and potential reporting bias associated with spontaneous adverse event reporting systems. However, their large sample sizes and consistency of signal across multiple analyses strengthened the reliability of observed associations.

Hospital-based cohort studies were constrained by their retrospective design, potential selection bias, and limited sample sizes in some cases. Nevertheless, these studies provided detailed clinical, biochemical, and outcome data that complemented the broader population-level findings from pharmacovigilance analyses. No included study was judged to have a serious or high risk of bias.

DISCUSSION

This systematic review summarizes observational and pharmacovigilance evidence on SGLT2 inhibitor–associated euglycemic diabetic ketoacidosis in non-perioperative settings. The main finding is that euDKA is not limited to surgical or fasting-related perioperative contexts but also occurs in routine medical settings, including acute infection, reduced oral intake, dehydration, insulin omission, and emergency or inpatient care. Across the included studies, euDKA represented a clinically relevant phenotype among SGLT2 inhibitor–associated DKA cases and was consistently characterized by lower presenting glucose levels despite clinically significant ketoacidosis. These findings emphasize that the absence of marked hyperglycemia should not reassure clinicians when patients using SGLT2 inhibitors present with metabolic acidosis or nonspecific gastrointestinal symptoms.

The findings of this review are generally consistent with previous reviews describing SGLT2 inhibitor–associated DKA as a rare but important safety concern. Earlier reviews have emphasized

the biological plausibility of SGLT2 inhibitor–related ketogenesis, the role of precipitating stressors, and the diagnostic challenge created by near-normal glucose levels. However, many previous syntheses included case reports, perioperative cases, or broad DKA populations without specifically isolating non-perioperative euDKA. The present review adds to the literature by focusing specifically on observational and pharmacovigilance evidence from non-perioperative settings, thereby providing a more practice-oriented synthesis relevant to emergency departments, medical wards, intensive care units, and outpatient sick-day management.

The mechanistic basis for SGLT2 inhibitor–associated euDKA is well supported by existing experimental and clinical evidence. SGLT2 inhibition promotes glycosuria, leading to reductions in circulating insulin levels and relative hyperglucagonemia, thereby shifting substrate utilization toward lipid oxidation and ketone body production.[4,5] This metabolic shift is further amplified during periods of physiological stress, such as infection, dehydration, or caloric restriction, which were consistently identified as precipitating factors in the included studies. Continued renal glucose excretion during ketoacidosis blunts the hyperglycemic response, allowing significant ketoacidosis to develop in the presence of near-normal plasma glucose levels[3]. These mechanisms collectively explain the atypical biochemical presentation of euDKA and its propensity to evade early detection. From a pathophysiological perspective, SGLT2 inhibitor–associated euglycemic diabetic ketoacidosis represents a unique metabolic state driven by alterations in glucose handling, hormonal balance, and substrate utilization. By inhibiting renal glucose reabsorption in the proximal tubules, SGLT2 inhibitors induce persistent glycosuria, reducing circulating plasma glucose and thereby decreasing endogenous insulin secretion. At the same time, these agents have been shown to increase glucagon secretion, thereby reducing the insulin-to-glucagon ratio and favoring lipolysis and hepatic ketogenesis.

The decline in insulin levels limits glucose utilization and removes the inhibitory effect of insulin on hormone-sensitive lipase, thereby promoting free fatty acid release from adipose tissue. These free fatty acids are transported to the liver, where they undergo β-oxidation and are converted into ketone bodies. In parallel, SGLT2 inhibitors may enhance renal reabsorption of ketone bodies, further increasing circulating ketone concentrations. Importantly, the ongoing urinary excretion of glucose blunts the expected hyperglycemic response during ketoacidosis, allowing significant metabolic acidosis to develop even with normal or only mildly elevated plasma glucose levels. This metabolic vulnerability is further amplified in non-perioperative clinical settings by common precipitating factors, including acute infection, dehydration, reduced carbohydrate intake, and insulin omission. These stressors increase counter-regulatory hormone release and exacerbate insulin deficiency, accelerating ketone body production. Consequently, euglycemic diabetic ketoacidosis may evolve insidiously, delaying diagnosis and treatment due to the absence of marked hyperglycemia, despite metabolic severity comparable to classical diabetic ketoacidosis.

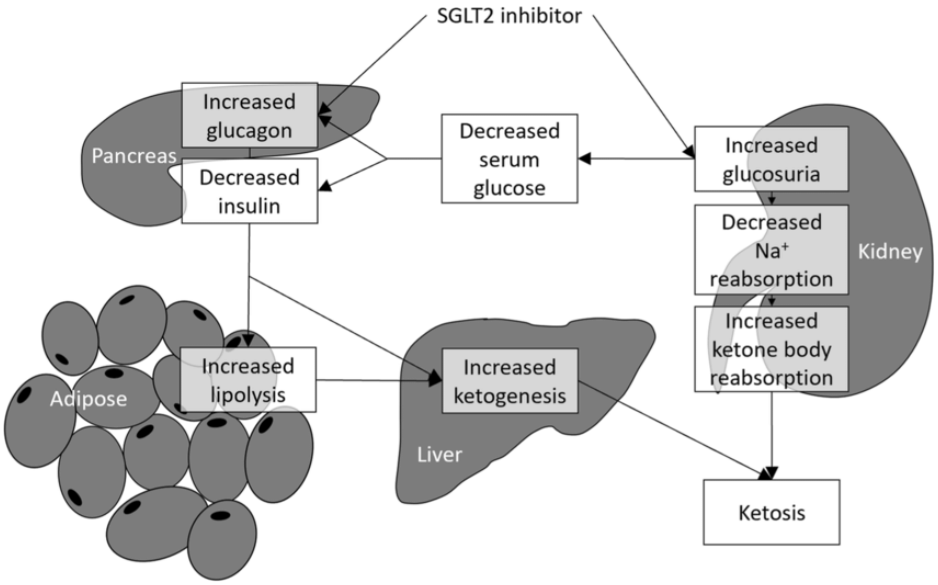

Figure 2. Pathophysiological mechanisms of SGLT2 inhibitor–associated euglycemic diabetic ketoacidosis

SGLT2 inhibitors reduce renal glucose reabsorption, leading to persistent glycosuria and lower circulating plasma glucose levels. This results in decreased insulin secretion and a relative increase in glucagon, shifting the insulin-to-glucagon ratio toward lipolysis and hepatic ketogenesis. Enhanced free fatty acid oxidation and ketone body production occur, while continued urinary glucose excretion masks hyperglycemia during ketoacidosis. Common non-perioperative stressors such as acute infection, reduced carbohydrate intake, dehydration, and insulin omission further exacerbate this metabolic imbalance, allowing significant ketoacidosis to develop despite normal or mildly elevated plasma glucose levels.

The precipitating factors identified in this review were notable for their consistency across diverse healthcare settings and study designs. Acute infection emerged as the most frequently reported trigger, reflecting the combined effects of stress hormone release, insulin resistance, and reduced oral intake during illness.[8,9] Starvation or carbohydrate restriction, whether intentional or illness-related, was also commonly implicated and may synergize with SGLT2 inhibitor–induced glycosuria to accelerate ketogenesis. Insulin omission or dose reduction, either deliberate or inadvertent, further exacerbates this metabolic imbalance. Importantly, all included studies focused on non-perioperative contexts, reinforcing that euDKA is not confined to surgical or fasting states but may occur during routine medical illness or hospital admission.

Pharmacovigilance analyses provided complementary evidence supporting the association between SGLT2 inhibitors and euDKA at a population level. Disproportionality analyses using large adverse event reporting databases demonstrated strong and consistent safety signals linking SGLT2 inhibitors to euDKA.[9–11] While these studies are limited by under-reporting, reporting bias, and lack of granular clinical data, the reproducibility of signals across independent analyses strengthens causal inference. Moreover, pharmacovigilance data capture real-world prescribing patterns and patient behaviors that may not be fully represented in clinical trials, enhancing the external validity of these findings.

Clinical outcomes associated with euDKA were generally favorable with respect to mortality, which remained low in both cohort and pharmacovigilance studies.[9,12,13] However, the need for intensive care admission and the duration of hospitalization were variable and, in some studies, comparable between euDKA and hyperglycemic DKA. These findings suggest that euDKA should not be regarded as a milder variant of DKA solely on the basis of lower glucose levels. Furthermore, management of euDKA presents unique therapeutic challenges, as insulin administration must be balanced against the risk of hypoglycemia in the setting of normal or mildly elevated glucose concentrations.[14] This complexity underscores the importance of early recognition and tailored management strategies.

The focused non-perioperative scope of this review is clinically relevant because many real-world euDKA episodes occur outside surgical pathways, where standardized perioperative SGLT2 inhibitor withholding protocols may not apply. In routine medical practice, triggers such as infection, vomiting, dehydration, carbohydrate restriction, and insulin omission are common and may develop unpredictably. This creates a different prevention challenge compared with elective surgery, where medication withholding can be planned in advance. Therefore, the findings support a broader approach to risk mitigation that extends beyond perioperative guidance and includes outpatient counseling, emergency department recognition, and inpatient medication review.

Nevertheless, the available evidence should be interpreted cautiously. Most included studies were retrospective cohorts or pharmacovigilance analyses, which limits causal inference and increases the possibility of selection bias, reporting bias, and incomplete clinical data. Pharmacovigilance studies are useful for detecting safety signals, but they cannot provide reliable incidence estimates because denominator data are unavailable and adverse events may be under-reported. Hospital-based cohorts provide more detailed biochemical and clinical information, but their findings may not fully represent milder cases managed outside the hospital. Therefore, the current evidence suggests a strong association between SGLT2 inhibitor use and euDKA in non-perioperative settings, but it does not establish definitive causality or a precise population-level risk estimate.

From a clinical perspective, the most important implication is that glucose levels alone are insufficient to rule out DKA in patients receiving SGLT2 inhibitors.[15-18] Patients with euDKA may present with nausea, vomiting, abdominal pain, malaise, tachypnea, or dehydration while having normal or only mildly elevated plasma glucose. Therefore, clinicians should consider early assessment of serum or urine ketones, venous or arterial blood gas, bicarbonate, and anion gap in SGLT2 inhibitor users with unexplained illness or metabolic derangement. This is particularly important during infection, poor oral intake, dehydration, prolonged fasting, low-carbohydrate dieting, or insulin dose reduction. Early recognition may prevent delayed insulin therapy, inappropriate reassurance based on glucose values, and progression to more severe acidosis.[19,20]

The management of euDKA also differs from routine hyperglycemic DKA in several practical aspects.[19-21] Because plasma glucose is not markedly elevated, insulin infusion may need to be accompanied earlier by dextrose-containing fluids to suppress ketogenesis while preventing hypoglycemia. SGLT2 inhibitors should be discontinued during the acute episode, and treatment should focus on fluid resuscitation, correction of electrolyte abnormalities, insulin therapy, and close monitoring of acid–base status until anion gap closure. Preventive strategies are equally important, particularly patient education on sick-day rules, temporary drug discontinuation during acute illness or during periods of reduced intake, avoidance of prolonged fasting, and prompt medical evaluation when symptoms suggest ketoacidosis.[13,15]

Several limitations of the current evidence base should be acknowledged. The included studies were predominantly retrospective and observational, limiting the ability to establish causality and introducing potential selection and information biases. Definitions of euDKA varied across studies, and outcome reporting was heterogeneous, precluding quantitative synthesis. Pharmacovigilance studies, while valuable for signal detection, lack denominator data and detailed clinical characterization. Additionally, most studies focused on hospitalized patients, potentially underestimating the burden of milder euDKA cases managed in outpatient settings.

Future research should prioritize prospective studies to better quantify the incidence of euDKA across different patient populations and clinical contexts. Identification of high-risk subgroups, including patients with low carbohydrate intake, insulin-deficient phenotypes, or recurrent intercurrent illness, may enable more targeted preventive strategies. Further work is also needed to refine management protocols specific to euDKA, balancing effective resolution of ketoacidosis with minimization of treatment-related hypoglycemia. As the clinical indications for SGLT2 inhibitors continue to expand, improving awareness, early detection, and prevention of euDKA will remain essential to optimizing patient safety.

CONCLUSION

The available evidence suggests a strong association between SGLT2 inhibitor use and euglycemic diabetic ketoacidosis in non-perioperative settings. EuDKA may occur during routine medical illness, particularly in the presence of infection, reduced oral intake, dehydration, or insulin omission. Although glucose levels are normal or only mildly elevated, euDKA may still present with clinically significant ketoacidosis and require hospital-based management. Therefore, clinicians should maintain a high index of suspicion, perform early assessment of ketones and acid–base status, and temporarily discontinue SGLT2 inhibitors during acute illness or reduced intake. Further prospective studies are required to clarify the incidence, risk factors, and prevention strategies for euDKA in non-perioperative clinical practice.

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