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Sodium Glucose Co-Transporters Induced Euglycemic Diabetic Ketoacidosis: A Review

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ABSTRACT

Background: Sodium–glucose cotransporter-2 (SGLT-2) inhibitors are commonly prescribed medications for lowering blood sugar, offering significant cardiovascular and kidney protection for individuals with type 2 diabetes mellitus (T2DM). Despite their beneficial effects on heart and metabolism, increased clinical use has uncovered a rare but serious side effect—euglycemic diabetic ketoacidosis (euDKA). This condition is marked by high anion-gap metabolic acidosis and notable ketosis without severe hyperglycemia, presenting unique diagnostic and treatment challenges. **Objective:** The aim is to thoroughly examine the pharmacology of SGLT-2 inhibitors and compile current evidence on the pathophysiology, biochemical characteristics, epidemiology, risk factors, clinical presentation, diagnosis, management, and prevention of euDKA associated with SGLT-2 inhibitors.**Methods:**A narrative review of existing literature, including randomized clinical trials, observational cohort studies, case series, mechanistic studies, and regulatory safety communications, was performed to summarize the current understanding of euDKA.**Results:**SGLT-2 inhibitors lower blood glucose by promoting renal glucose excretion independent of insulin. However, they disrupt the insulin–glucagon balance, increase lipolysis and liver ketogenesis, and cause osmotic diuresis with fluid loss. These processes create a metabolic environment that encourages ketosis even when glucose levels are normal or only slightly elevated (<250 mg/dL). Although the overall occurrence of euDKA is low, the relative risk is higher compared to other glucose-lowering drugs, especially during infection, fasting, surgery, dehydration, or reduced insulin doses. Early detection requires ketone testing and acid–base evaluation. Treatment is similar to standard DKA therapy. **Conclusion:** While SGLT-2 inhibitor–related euDKA is rare, it is clinically important. With proper risk assessment, patient education, and monitoring, the significant cardiovascular and renal benefits of SGLT-2 inhibitors generally surpass the potential risks.

Keywords: SGLT-2 inhibitors, euglycemic diabetic ketoacidosis,type 2 diabetes mellitus, insulin-glucagon imbalance, ketogenesis.

1. INTRODUCTION

A novel category of glucose-lowering medications known as sodium-glucose cotransporter-2 (SGLT2) inhibitors works by specifically blocking SGLT2 proteins in the proximal renal tubules, which lowers glucose reabsorption and increases urine glucose excretion [1, 3, 4]. Without directly inducing insulin secretion, this insulin-independent mechanism effectively lowers plasma glucose levels [2, 5]. SGLT2 inhibitors have expanded their role beyond traditional glucose lowering by promoting modest weight loss, lowering blood pressure, and having positive hemodynamic and metabolic effects in addition to improving glycemic control [2].

SGLT2 inhibitors are now a mainstay treatment for type 2 diabetes mellitus (T2DM) because of strong evidence of their advantages for the kidneys and heart [7, 8]. Heart failure hospitalization rates have decreased, the progression of chronic kidney disease has slowed, and overall cardiovascular outcomes have improved, according to large cardiovascular outcome trials [7, 9, 11]. As a result, SGLT2 inhibitors are now advised by international diabetes guidelines, especially for individuals with type 2 diabetes who also have heart failure, chronic kidney disease, or cardiovascular disease [10]. SGLT2 inhibitors have been used off-label in certain patients as supplements to insulin therapy, despite the fact that they are not authorized for routine use in type 1 diabetes mellitus (T1DM) [12, 16]. These medications have shown advantages in T1DM, including improved postprandial glucose control, decreased insulin requirements, decreased glycemic variability, and weight loss [13, 14, 15]. However, there are significant safety concerns because this off-label use has been linked to an increased risk of ketoacidosis [17]. After SGLT2 inhibitor therapy was widely used in clinical settings, post-marketing surveillance and published case reports revealed euglycemic diabetic ketoacidosis (EDKA) as an uncommon but dangerous side effect [18]. High anion-gap metabolic acidosis, ketonemia or ketonuria, and only slightly elevated or even normal blood glucose levels (usually less than 250 mg/dL) are characteristics of EDKA as opposed to classical diabetic

ketoacidosis [18, 19]. The pathophysiology includes decreased insulin levels in the blood and elevated glucagon secretion brought on by SGLT2 inhibition, which increases ketogenesis and lipolysis [20]. Concurrent glycosuria conceals the hyperglycemia that usually warns medical professionals of diabetic ketoacidosis by lowering plasma glucose concentrations [21]. Prolonged fasting, acute illness or infection, perioperative stress, reduced or missed insulin doses, dehydration, excessive alcohol consumption, and adherence to very-low-carbohydrate or ketogenic diets are some of the frequently reported precipitating factors for SGLT2 inhibitor-associated EDKA [22, 23]. Importantly, because SGLT2 inhibition has long-lasting pharmacodynamic effects, EDKA may still happen even after the medication is temporarily stopped [24].

EDKA's peculiar appearance makes diagnosis difficult and may cause treatment to be delayed, which raises the risk of morbidity and perhaps deadly consequences [25]. Regulatory organizations, including the U.S. Food and Drug Administration, have published safety warnings emphasizing the danger of ketoacidosis with SGLT2 inhibitors in response to mounting data [26]. Increased clinician awareness is crucial as the use of these agents grows in endocrinology, cardiology, nephrology, and primary care [27, 28]. Crucial tactics to reduce this risk include early symptom detection, suitable patient selection, patient education, brief withdrawal during times of physiological stress, and timely ketone monitoring [29]. Therefore, guaranteeing the safe and efficient use of this treatment class requires an understanding of SGLT2 inhibitor-induced EDKA [30].

2. Materials and Methods

2.1 Study Design

This study was designed as a **narrative review** to summarize and synthesize current evidence on the pharmacology of sodium–glucose cotransporter-2 (SGLT-2) inhibitors and their association with euglycemic diabetic ketoacidosis (euDKA), including pathophysiology, clinical presentation, diagnosis, management, and prevention.

2.2 Data Sources and Search Strategy

A comprehensive literature search was conducted using electronic databases, including **PubMed, Scopus, Google Scholar, and Web of Science**, to identify relevant studies published between **2010 and 2025**.

The search strategy incorporated a combination of keywords and Medical Subject Headings (MeSH) terms such as *"euglycemic diabetic ketoacidosis," "euDKA," "SGLT-2 inhibitors," "diabetic ketoacidosis," "ketogenesis,"* and *"β-hydroxybutyrate."* These terms were used individually and in combination.

2.3 Inclusion and Exclusion Criteria

Inclusion Criteria:

Studies were included if they:

- Were published in English
- Included randomized controlled trials, observational studies, case reports, case series, or review articles
- Focused on euDKA and/or SGLT-2 inhibitor–associated ketoacidosis
- Reported data on pathophysiology, clinical features, diagnosis, or management

Exclusion Criteria:

Studies were excluded if they:

- Were non-English publications
- Were unrelated to euDKA or SGLT-2 inhibitors
- Included conference abstracts without full text

- Were duplicate or irrelevant records

2.4 Study Selection

All retrieved articles were initially screened based on titles and abstracts. Full-text articles of potentially relevant studies were then assessed for eligibility according to the predefined inclusion and exclusion criteria. Duplicate records were removed during the selection process.

2.5 Data Extraction and Synthesis

Relevant data from the included studies were extracted and categorized into key domains, including pharmacology, pathophysiology, biochemical characteristics, epidemiology, risk factors, clinical presentation, diagnosis, management, and prevention of euDKA.

A qualitative synthesis approach was employed to integrate findings and provide a comprehensive overview of the current evidence.

3. PHARMACOLOGY OF SGLT2 INHIBITORS

3.1. Mechanism of Action

1. Renal Glucose Reabsorption Blockade

Under normal physiological conditions, about 90% of the glucose filtered by the kidneys is reabsorbed in the proximal convoluted tubule through the sodium–glucose cotransporter-2 (SGLT2), while the remaining 10% is reabsorbed by SGLT1 in the distal segment [31]. SGLT2 inhibitors specifically target and block this transporter, leading to decreased glucose reabsorption in the kidneys and increased glucose excretion in the urine [32]. This process operates independently of pancreatic β-cell function and insulin sensitivity, making it effective for lowering glucose levels even in the later stages of type 2 diabetes mellitus (T2DM).

SGLT2 inhibitors facilitate the continuous removal of glucose through urine by lowering the renal threshold for glucose excretion, which in turn decreases both fasting and postprandial plasma glucose levels [33]. Notably, since this process does not trigger insulin release, the inherent risk of hypoglycemia remains low when these drugs are used alone or alongside non-insulin treatments.

2. Effects on Glycosuria, Body Weight, and Blood Pressure

Inhibiting SGLT2 results in continuous glycosuria, leading to a daily energy deficit of about 200–300 kcal [34]. This negative energy balance aids in a modest yet ongoing reduction in weight, mainly due to the loss of fat mass rather than lean muscle. Furthermore, the osmotic diuresis caused by glycosuria encourages natriuresis and a slight contraction of plasma volume. These renal effects manifest clinically as decreases in both systolic and diastolic blood pressure, generally ranging from 3 to 6 mmHg, without a compensatory rise in heart rate. The combined impact on weight, blood pressure, and intravascular volume enhances the cardiometabolic profile of SGLT2 inhibitors [35].

3.2. Approved SGLT2 Inhibitor Agents

Empagliflozin, dapagliflozin, canagliflozin, and ertugliflozin are the SGLT2 inhibitors currently approved for use. While these drugs operate through a similar mechanism, they exhibit slight variations in pharmacokinetics, SGLT2 selectivity, and clinical outcomes. Empagliflozin and dapagliflozin have the strongest evidence supporting their cardiovascular and renal benefits [27, 36]. Canagliflozin was the first in this category to show renal protection, although early studies linked it to a higher rate of certain adverse effects. Ertugliflozin has proven effective in controlling blood sugar and providing metabolic benefits, but its long-term outcome data are relatively sparse [37].

3.3. Therapeutic Benefits

1. Cardiovascular and Renal Protection

A major advancement with SGLT2 inhibitors is their proven cardiovascular and renal protective effects, which occur independently of blood sugar control. Large-scale randomized cardiovascular outcome trials have consistently shown reductions in heart failure hospitalizations, the progression of chronic kidney disease, and declines in estimated glomerular filtration rate (eGFR) [38].

The restoration of tubuloglomerular feedback and decreases in intraglomerular pressure caused by afferent arteriolar vasoconstriction are responsible for the renal advantages [39]. Reductions in albuminuria, oxidative stress, inflammation, and renal hypoxia are other causes. These advantages show a paradigm shift in the use of SGLT2 inhibitors as disease-modifying agents rather than just glucose-lowering medications, and they apply to both patients with and without diabetes.

2. Glycemic and Metabolic Effects

From a metabolic perspective, SGLT2 inhibitors reduce glycated hemoglobin (HbA1c) by roughly 0.5–1.0%, and their effectiveness is sustained over a range of diabetes durations [40]. They lower glycemic variability, postprandial glucose excursions, and fasting plasma glucose [41]. Modest increases in insulin sensitivity, decreases in blood uric acid levels, and positive effects on lipid profiles—including slight increases in high-density lipoprotein cholesterolare further metabolic advantages.

SGLT2 inhibitors have been used off-label as an adjuvant therapy to insulin in type 1 diabetes mellitus (T1DM), which has increased time-in-range, decreased insulin requirements, and led to weight loss. However, the increased risk of diabetic ketoacidosis, especially euglycemic diabetic ketoacidosis, outweighs these advantages, preventing their widespread usage in this population [42].

4. DEFINITION

Patients with type 1 or type 2 diabetes mellitus may develop euglycemic diabetic ketoacidosis (EDKA), a clinical syndrome marked by euglycemia (blood glucose < 250 mg/dL) in the presence of severe metabolic acidosis (arterial pH < 7.3, serum bicarbonate < 18 mEq/L) and ketonemia, even in the absence of the hyperglycemia characteristic of classic diabetic ketoacidosis. [43]

4.1 Pathophysiology

Euglycemic diabetic ketoacidosis (EDKA) is a distinct metabolic complication characterized byketoacidosis with normal or mildly elevated blood glucose levels**,** commonly associated with sodium–glucose cotransporter-2 (SGLT-2) inhibitor use. Its pathophysiology involves a combination of relative insulin deficiency, increased counter-regulatory hormones, and enhanced ketogenesis**.**

1. Altered Insulin–Glucagon Ratio

A central mechanism in EDKA is the reduction in the insulin-to-glucagon ratio. SGLT-2 inhibitors promote urinary glucose excretion, leading to decreased insulin secretion. Simultaneously, glucagon secretion increases, further aggravating this imbalance. This hormonal shift promotes lipolysis and hepatic ketone production [44,45].

2. Relative Insulin Deficiency

Despite near-normal glucose levels, insulin concentrations may be inadequate to suppress lipolysis and ketogenesis. Patients may also reduce insulin doses due to apparent glycemic control, further contributing to ketone body formation without significant hyperglycemia [45].

3. Enhanced Lipolysis and Ketogenesis

Reduced insulin action and elevated counter-regulatory hormones stimulate lipolysis, releasing free fatty acids. These are converted in the liver via β-oxidation into ketone bodies, primarily β-hydroxybutyrate and acetoacetate, resulting in high anion gap metabolic acidosis [44,45].

4. Reduced Carbohydrate Availability

Continuous glucosuria induced by SGLT-2 inhibitors leads to decreased carbohydrate availability, mimicking a starvation-like state. This metabolic shift promotes fat oxidation and increases ketone production [45].

5. Dehydration and Volume Depletion

Osmotic diuresis due to glucosuria causes dehydration and reduced renal perfusion. This impairs ketone clearance and stimulates counter-regulatory hormones, further worsening metabolic acidosis [46].

Biochemical Characteristics

EDKA is characterized by:

- Normal or mildly elevated plasma glucose levels
- High anion gap metabolic acidosis with low arterial pH
- Elevated ketone levels, particularly β-hydroxybutyrate

Notably, the severity of acidosis correlates more strongly with ketone accumulation than with glucose levels, which may delay diagnosis [47–50].

5. EPIDEMIOLOGY OF SGLT-2 INHIBITOR-ASSOCIATED euDKA

Euglycemic diabetic ketoacidosis is an uncommon but clinically important adverse effect of sodium–glucose cotransporter-2 (SGLT-2) inhibitors [51–54]. In a large multicenter retrospective cohort study involving 9,940 adults with type 2 diabetes treated with SGLT-2 inhibitors, diabetic ketoacidosis was identified in 43 patients (0.43%) over a five-year period. Among these DKA cases, euglycemic DKA accounted for the majority, occurring in 25 patients, which represents approximately 58% of all DKA events observed in this population [54].

Although the overall risk of DKA remains low [51–53], the findings highlight that when DKA occurs in patients receiving SGLT-2 inhibitors, it is more likely to present as euglycemic rather than hyperglycemic DKA (4). This atypical presentation may delay recognition and diagnosis, as patients do not exhibit the marked hyperglycemia traditionally associated with diabetic ketoacidosis [51,54].

Euglycemic DKA was observed across commonly prescribed SGLT-2 inhibitors, including canagliflozin, empagliflozin, and dapagliflozin, suggesting that this complication is a class effect rather than drug-specific [51–54]. While some variation in frequency between individual agents was noted, statistically significant differences were not demonstrated due to the small number of events [54].

Most cases occurred in patients with type 2 diabetes, the primary population receiving SGLT-2 inhibitors (52,54). Common precipitating factors included intercurrent infections and insulin omission or non-compliance, indicating that acute illness and reduced insulin availability play a key role in triggering euglycemic DKA in this setting [52,54].

Overall, this real-world cohort study demonstrates that SGLT-2 inhibitor associated euglycemic DKA is rare but represents the predominant form of DKA in affected users, underscoring the need for heightened clinical awareness despite relatively normal blood glucose levels [54].

6. RISK FACTORS FOR euDKA WITH SGLT-2 INHIBITORS

6.1 Patient related factors

Euglycemic diabetic ketoacidosis (euDKA) associated with SGLT-2 inhibitors is strongly influenced by several patient-related factors. Individuals with relative or absolute insulin deficiency, such as those with long-standing diabetes, reduced β-cell reserve, or latent autoimmune diabetes of adulthood, are particularly susceptible because SGLT-2 inhibitors lower plasma glucose and insulin secretion while increasing glucagon levels, thereby promoting ketogenesis. Reduction or omission of insulin therapy, often triggered by improved glucose readings after starting SGLT-2 inhibitors, further increases the risk [55].States of reduced carbohydrate availability, including prolonged fasting, starvation, very-low-carbohydrate or ketogenic diets, and excessive alcohol intake, shift metabolism toward fatty acid oxidation and ketone production. Physiological stressors such as acute illness, infection, surgery, trauma, or pregnancy increase counter-regulatory hormones and insulin requirements, predisposing to euDKA. Additionally, dehydration due to osmotic diuresis from glucosuria worsens insulin deficiency and enhances ketone formation. Collectively, these patient-related factors create a metabolic milieu favoring ketoacidosis despite normal or only mildly elevated blood glucose levels when SGLT-2 inhibitors are used [56, 57].

6.2 Drug-related factors

Drug-related risk factors have been identified that predispose patients to this complication. Because SGLT2 inhibitors lower blood glucose by increasing urinary glucose excretion, they can lead to relative insulin deficiency, and as a result clinicians or patients often reduce insulin doses, which decreases circulating insulin and encourages lipolysis and ketogenesis, increasing the likelihood of eDKA. Use of these agents off-label in type 1 diabetes or in patients with limited endogenous insulin secretory reserve (e.g., latent autoimmune diabetes of adulthood) also significantly raises risk because of diminished insulin availability [55]. Very low carbohydrate intake or ketogenic diets in combination with SGLT-2 inhibitor use further suppress insulin secretion and elevate glucagon, creating a metabolic environment favorable to ketone production. Situations that increase insulin demand or cause metabolic stress such as acute illness, surgery, trauma, fasting, or dehydration—can unmask this susceptibility by heightening counter-regulatory hormone levels and reducing effective insulin action. Additionally, epidemiologic observations suggest female sex may carry a higher risk, potentially due to sex-based differences in fuel utilization and lipolytic responses. These drug-related and medication-associated factors interact with the pharmacological effects of SGLT2 inhibition to promote ketogenesis even when blood glucose remains normal or only modestly elevated, characteristic of euglycemic DKA [58].

6.3 Predisposing Conditions

Predisposing factors described in the literature include acute medical illnesses such as infections, major surgery, trauma, or severe physiological stress, which increase counter-regulatory hormones and promote lipolysis. Reduced carbohydrate intake due to prolonged fasting, starvation, vomiting, or adherence to low-carbohydrate or ketogenic diets further enhances ketone body production. Dehydration and volume depletion, often related to poor oral intake or gastrointestinal losses, also contribute by worsening insulin deficiency [59]. In addition, reduction or omission of insulin therapy, especially in patients with limited pancreatic β-cell reserve, significantly increases the risk. Perioperative continuation of SGLT-2 inhibitors or inadequate discontinuation before surgery has been frequently reported as a trigger. Together, these factors, combined with the SGLT-2 inhibitor induced reduction in plasma glucose and insulin levels and relative increase in glucagon, create a metabolic state favoring euglycemic diabetic ketoacidosis despite near-normal blood glucose levels [60].

7. CLINICAL PRESENTATION

7.1 Symptoms

Euglycemic diabetic ketoacidosis (EDKA) associated with SGLT-2 inhibitor use presents with many of the typical symptoms of diabetic ketoacidosis, such as nausea, vomiting, abdominal pain, malaise, fatigue, shortness of breath, and tachycardia, but without the marked hyperglycemia that usually prompts clinicians to consider DKA. Patients often have normal or only mildly elevated blood glucose levels (<200 mg/dL) because SGLT-2 inhibitors increase urinary glucose excretion, masking the high glucose levels seen in classic DKA and leading to a diagnostic challenge[61]. Despite this euglycemia, there is significant metabolic acidosis with an elevated anion gap and elevated serum ketones (particularly beta-hydroxybutyrate), reflecting ongoing ketoacidosis. Because of the absence of pronounced hyperglycemia, patients typically do not experience classic osmotic symptoms such as polyuria and polydipsia, and both patients and clinicians may be misled by seemingly “Normal” glucose measurements, delaying diagnosis and treatment. A high index of suspicion is therefore crucial in anyone on SGLT-2 inhibitors who presents with these nonspecific systemic and gastrointestinal symptoms, especially in the context of triggers like illness, reduced food intake, or perioperative stress [62].

7.2 Red flags

The FDA has updated the labels for SGLT2 inhibitors a class of diabetes medicines that includes drugs like canagliflozin, dapagliflozin, and empagliflozin, to add a clear warning about the risk of ketoacidosis, including a specific form called euglycemic diabetic ketoacidosis (euDKA), in people taking these medications. The revised labeling highlights that ketoacidosis can occur even when blood glucose levels are not very high (for example, below 250 mg/dL), which is the characteristic feature of euDKA and can make the condition harder to recognize because high blood sugar is usually expected with diabetic ketoacidosis. Patients and clinicians are advised to be alert for symptoms of ketoacidosis such as nausea, vomiting, abdominal pain, unusual tiredness, and trouble breathing even if blood glucose readings are near normal, because these may signal too much acid in the blood. If such symptoms occur while taking an SGLT2 inhibitor, the instruction is to stop the medication and seek immediate medical attention, and where possible, to check for ketones in the urine, since early detection and treatment are critical. The FDA also notes that certain situations such as surgery, illness with reduced food intake, or changes in insulin dosing can increase the risk of ketoacidosis in people taking SGLT2 inhibitors, reinforcing that euDKA is a serious, red-flag adverse effect that requires prompt recognition and management even in the absence of marked hyperglycemia [63].

8. DIAGNOSIS

When a patient has severe anion-gap metabolic acidosis, considerable blood ketones, and a blood glucose level below 250 mg/dL, they are diagnosed with euglycemic diabetic ketoacidosis (EDKA). [77, 82] The diagnosis cannot be based solely on glucose because the patient does not exhibit extremely high blood sugar levels, unlike in classical DKA. [79] Clinicians are forced to rely on laboratory testing instead. Patients on SGLT-2 inhibitors, pregnant women, people fasting for extended periods of time, people with infections, and people experiencing acute medical stress are the groups most likely to experience EDKA [80, 81]. Since many instances are initially overlooked because of normal glucose tests, early diagnosis is crucial.

8.1 LABORATORYEVALUATION

➢ SERUM KETONES

Since serum β-hydroxybutyrate is the primary ketone produced during ketoacidosis, it is the most crucial sign for diagnosing EDKA [83]. Levels are considerably elevated in the majority of patients and aid in verifying actual ketosis. Blood ketone testing is recommended to prevent underestimating the severity of the problem because urine ketone strips can occasionally be deceptive because they detect acetoacetate rather than β-hydroxybutyrate [83, 84].

➢ ARTERIAL/VENOUSBLOOD GAS

To verify acidosis, blood gas analysis is necessary. Venous samples are typically preferable; however, arterial samples can also be used. Metabolic acidosis is indicated by the majority of patients' low bicarbonate (≤18mEq/L) and decreased pH (≤7.30) [85]. Repeat testing is useful when clinical suspicion is still high because the acidosis may occasionally be modest, particularly in the early stages of the illness [86].

➢ ELECTROLYTESANDANIONGAP

High anion-gap metabolic acidosis is typically revealed by electrolyte testing. In general, the anion gap is greater than 12 mEq/L [87].At presentation, potassium levels may seem normal or slightly elevated, but overall body potassium is actually low and may drop even more after insulin treatment starts, so close observation is crucial [88]. BUN and creatinine may also be high because many patients are dehydrated.

➢ BLOODGLUCOSE

Blood glucose levels that arenormaloronlyslightlyelevated-typicallylessthan250 mg/dL are a distinctive characteristic of EDKA [89]. This occurs as a result of either decreased glucose synthesis during fasting or glucose loss through urine, particularly with SGLT2 inhibitor medication. Even when glucose appears "normal," physicians must remember to assess ketones because sugar is not noticeably increased.

8.2 DIFFERENTIAL DIAGNOSIS

➢ STARVATION KETOSIS

Following extended fasting or a decrease in carbohydrate consumption, starvation ketosis takes place. Although acidosis is often minor, ketones may be present. pH stays above 7.30, and bicarbonate levels are often higher than 18 mEq/L [90]. Usually, glucose is either low or normal. The key aspect is that, in contrast to EDKA, starvation ketosis rapidly improves if carbs are administered [91].

➢ ALCOHOLIC KETOACIDOSIS

Alcoholic ketoacidosis is more common in long-term drinkers who consume large amounts of alcohol and then throw up or eat poorly [92]. Significant **ketonemia** with wildly fluctuating glucose levels develops in these people. They frequently suffer from electrolyte imbalances and dehydration. It can be distinguished from EDKA by a significant alcohol history and quick recovery with dextrose [93].

➢ **LACTIC ACIDOSIS**

Lactic acidosis is brought on by oxygen deprivation, severe illnesses like sepsis, shock, liver failure, or some medications. Ketones are not the primary problem in this disease; instead, lactate levels are markedly high [94]. Lactic acidosis can be distinguished from EDKA by the presence of extremely high lactate and characteristics of tissue hypoperfusion.

➢ **TOXIC INGESTIONS**

High anion-gap acidosis can also result after poisoning with chemicals such as methanol, ethylene glycol, salicylates, or isopropanol [95]. These patients may exhibit high osmolar gaps and frequently have particular clinical symptoms, such as respiratory issues, kidney involvement, or visual difficulties. Unlike EDKA, these toxins typically have a known history of intake and do not predominantly produce ketone-driven acidosis [96].

9. PATHOPHYSIOLOGY LINKINGSGLT-2INHIBITORSTOEUGLYCEMIC DIABETIC KETOACIDOSIS (euDKA)

- **Renal Glucose Excretion Leading to Reduced Insulin Secretion**

Increased glucose loss through urine is how SGLT-2 inhibitors function. Blood glucose levels decrease because glucose is constantly eliminated. The pancreas is signaled to decrease insulin release by this decreased glucose level. This relative decrease is sufficient to disrupt normal metabolism even though insulin is not entirely missing [97]. Fat breakdown is generally suppressed by insulin; thus, when insulin levels fall, fat breakdown rises, favoring the formation of ketones even in the presence of normal blood glucose levels.

- **Elevated Glucagon Levels**

SGLT-2inhibitorscausepancreaticα-cellstosecretemoreglucagoninadditiontolessinsulin. The glucagon-to-insulin ratio rises as a result. The liver is stimulated by glucagon to create ketone bodies and glucose [98]. This hormonal imbalance contributes significantly to the development of euDKA by aggressively promoting ketogenesis.

- **Increased Fatty Acid Oxidation**

In adipose tissue, lipolysis is stimulated by both increased glucagon and decreased insulin. Free fattyacids are liberated into the bloodstream and carried to the liver in large quantities. These fatty acids go viaβ-oxidation in the liver, which results in an over abundance of ketone molecules like acetoacetate and β-hydroxybutyrate. Metabolic acidosis is directly caused by the buildup of these ketones.

- **Volume Depletion and Enhanced Counter-Regulatory Hormone Release**

Dehydration and volume depletion result from osmotic diuresis, which is caused by glucose loss in the urine. Catecholamines, cortisol, and growth hormone are among the counter-regulatory hormones that are triggered by this. These hormones stimulate lipolysis and ketone generation while also decreasing insulin sensitivity. Additionally, dehydration worsens ketonemia and acidosis by reducing renal clearance of ketones.

- **Shift to Ketone Utilization by Peripheral Tissues**

SGLT-2 inhibitors encourage the body's metabolism to change in favor of using ketones as a substitute energy source, particularly in the heart and muscles. Although this change aids in supplying energy when glucose is scarce, the liver produces more ketones than it uses. Because of this, even when blood glucose levels are normal or slightly increased, ketones continue to buildup in the blood, resulting in high anion-gap metabolic acidosis and chronic ketonemia[99].

10. MANAGEMENT OF SGLT-2 INHIBITOR-ASSOCIATED euDKA

10.1 Acute Management

Management of SGLT-2 inhibitor–associated euglycemic diabetic ketoacidosis (EDKA) should begin with immediate discontinuation of the SGLT-2 inhibitor once the diagnosis is suspected or confirmed. Treatment principles are similar to conventional diabetic ketoacidosis despite normal or mildly elevated blood glucose levels. Aggressive intravenous fluid resuscitation

with isotonic crystalloids is initiated to correct dehydration and improve tissue perfusion. Because patients are euglycemic, dextrose-containing fluids (e.g., D5W or D10W) are added early to prevent hypoglycemia and to allow continued insulin administration [63, 64]. Continuous intravenous insulin infusion is essential to suppress lipolysis and ketogenesis and to correct metabolic acidosis. Electrolyte abnormalities, particularly potassium depletion, must be anticipated and corrected appropriately, with careful replacement guided by laboratory values. Any precipitating factors such as infection, prolonged fasting, dehydration, surgery, or reduced insulin doses should be promptly identified and treated [55, 65].

10.2 Monitoring

Close and frequent monitoring is critical during treatment of SGLT-2 inhibitor–associated EDKA. Blood glucose levels should be checked frequently (often every 1–2 hours initially) to avoid hypoglycemia while on insulin therapy. Serum or capillary ketone levels (β-hydroxybutyrate) should be monitored serially to assess resolution of ketosis [63]. Serum electrolytes, bicarbonate, anion gap, and acid–base status should be measured every 4–6 hours in the acute phase. Vital signs, fluid balance, and overall clinical status must be closely observed. Monitoring should continue even after apparent resolution, as the pharmacologic effects of SGLT-2 inhibitors may persist and predispose to recurrent ketosis [64].

10.3 When to restart SGLT-2 inhibitors

SGLT-2 inhibitors should not be restarted during the acute episode of euglycemic DKA or while ketosis or metabolic acidosis persists. Reinitiation may be considered only after complete resolution of ketoacidosis, defined by normalization of the anion gap, pH, bicarbonate levels, and serum ketones, along with stable clinical condition and normal oral intake. All precipitating factors must be corrected, and the patient should be educated about sick-day rules, carbohydrate intake, and early recognition of symptoms. The decision to restart therapy should be individualized and made cautiously, ideally in consultation with an endocrinologist, weighing the cardio-renal benefits of SGLT-2 inhibitors against the risk of recurrent EDKA [65,66].

11. DISCUSSION

11.1 Why EDKA is Often Missed

Euglycemic diabetic ketoacidosis (EDKA) is frequently underdiagnosed due to the absence of marked hyperglycemia, which is typically considered a hallmark feature of diabetic ketoacidosis. Clinicians may overlook the possibility of ketoacidosis when blood glucose levels are below 250 mg/dL, resulting in delayed diagnosis and initiation of treatment [42,67]. Furthermore, reliance on urine ketone testing contributes to missed or delayed detection, as these tests primarily identify acetone and acetoacetate but fail to detect β-hydroxybutyrate, the predominant ketone body in EDKA. The presence of non-specific symptoms such as nausea, vomiting, abdominal pain, and malaise further complicates the clinical picture, particularly in low-resource settings where routine ketone monitoring is not widely practiced.

In addition, SGLT-2 inhibitors contribute to diagnostic challenges by promoting glucosuria, which masks underlying insulin deficiency and creates a misleading perception of metabolic stability. Their prolonged pharmacological action may sustain ketogenesis even after drug discontinuation, thereby increasing the risk of delayed recognition or recurrence of metabolic acidosis [20,68,69].

11.2 Clinical Implications

With the expanding use of SGLT-2 inhibitors in the management of diabetes mellitus, heart failure, and chronic kidney disease, early recognition of EDKA has become increasingly important. Failure to promptly diagnose this condition can lead to prolonged hospitalization, increased morbidity, and severe metabolic complications [36,70]. Therefore, clinicians should maintain a high index of suspicion for EDKA, particularly in patients presenting with non-specific symptoms despite normal or mildly elevated blood glucose levels.

Incorporation of routine ketone monitoring, especially measurement of blood β-hydroxybutyrate, along with assessment of the anion gap in symptomatic patients, is essential for early detection. Particular attention should be given during stress conditions such as infection, prolonged fasting, or surgical procedures, which are known to precipitate EDKA. Preventive strategies, including temporary discontinuation of SGLT-2 inhibitors 3–4 days prior to elective surgery and during acute illness, have been recommended to minimize the risk of ketoacidosis [71,72,75].

11.3 Risk–Benefit Balance of SGLT-2 Inhibitors

SGLT-2 inhibitors have emerged as a cornerstone in the management of type 2 diabetes mellitus due to their well-established cardiovascular and renal benefits, including reduction in heart failure hospitalizations and slowing of chronic kidney disease progression. However, their use is associated with a small but clinically significant risk of EDKA [76,77]. Although the relative risk of diabetic ketoacidosis is increased in patients receiving SGLT-2 inhibitors, the absolute incidence remains low, and most reported cases occur in the presence of identifiable precipitating factors such as insulin omission, infection, surgery, or prolonged fasting.

Current evidence supports the continued use of SGLT-2 inhibitors with appropriate risk mitigation strategies, including careful patient selection and adequate patient education regarding early symptom recognition and sick-day management. EDKA should therefore be considered a preventable complication rather than an absolute contraindication to therapy. Individualized clinical decision-making is essential, particularly when considering reinitiation of SGLT-2 inhibitors following an episode of EDKA. Patients with underlying insulin deficiency or those at high risk may require closer monitoring or consideration of alternative therapeutic options [29,76,78].

CONCLUSION

SGLT-2 inhibitors offer significant cardiovascular and renal advantages in treating type 2 diabetes mellitus, yet they carry a rare but important risk of euglycemic diabetic ketoacidosis (euDKA). This condition is marked by high anion-gap metabolic acidosis and ketosis, even when glucose levels are nearly normal. Such an unusual presentation can delay diagnosis and increase morbidity if not quickly identified. Although the absolute risk is low, healthcare providers should remain alert, especially during times of physiological stress like infections, surgeries, fasting, or when insulin doses are reduced. Early ketone testing, educating patients, and proper perioperative discontinuation are crucial preventive measures. With careful patient selection and systematic monitoring, the overall cardiovascular and renal benefits of SGLT-2 inhibitors generally surpass the potential risk of euDKA.

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