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Sodium-glucose Cotransporter-2 (SGLT2) Inhibitors induced euglycemic diabetic ketoacidosis: A meta summary of case reports

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Juneja D et al. SGLT2 Inhibitors induced euglycemic DKA

ABSTRACT

Background: Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are commonly prescribed drugs to manage patients with diabetes mellitus (DM). These agents may rarely lead to the development of euglycemic diabetic ketoacidosis (EDKA), which may complicate the disease course of these patients.

Aim: To analyze the demographic profile, predisposing factors, symptomology, clinical interventions and outcomes of patients presenting with EDKA secondary to SGLT2i use by reviewing the published case reports and series.

Methods: We performed a systematic search from PubMed, Science Direct, Google Scholar and *Reference Citation Analysis* databases using the terms "canagliflozin" OR "empagliflozin" OR "dapagliflozin" OR "SGLT2 inhibitors" OR "Sodium-glucose cotransporter-2" AND "euglycemia" OR "euglycemic diabetic ketoacidosis" OR "metabolic acidosis". The inclusion criteria were (1) Case reports or case series with individual patient details; (2) Reported EDKA secondary to SGLT2i. Further, it was filtered for the literature published in English language and on adult (> 18 years). We excluded 1) Conference abstracts; 2) Case reports or series which did not have individual biochemical data. All the case reports and case series were evaluated. The

data were extracted for patient demographics, clinical symptomatology, clinical interventions, intensive care unit (ICU) course, need for organ support and outcomes.

Results: Overall, 108 case reports and 17 cases series with 169 unique patients that met all the inclusion criteria were included. The majority of patients were females (54.4%, n = 92), and the commonly reported symptoms were gastrointestinal (nausea/vomiting 65.1%, abdominal pain 37.3%) and respiratory (breathlessness 30.8%). One hundred and forty-nine (88.2%) patients had underlying type I diabetes, and the most commonly involved SGLT-2 inhibitor reported was empagliflozin, 46.8%. A triggering factor was reported in most patients (78.7%), the commonest being acute severe infection (37.9%), which included patients with sepsis, COVID-19 disease, other viral illnesses, and acute pancreatitis. 61.5% were reported to require intensive unit care, but only a minority of patients required organ support in the form of invasive mechanical ventilation (13%), vasopressors (6.5%) or renal replacement therapy (5.9%). The overall mortality rate was only 2.4%.

Conclusions: Patients on SGLT2i may rarely develop EDKA, especially in the presence of certain predisposing factors, including severe acute infections and after major surgery. The signs and symptoms of EDKA may be similar to that of DKA but with normal blood sugar levels, which may make diagnosis challenging. Outcomes of EDKA are good if recognized early and corrective actions are taken. Hence, physicians managing such patients must be aware of this potential complication and must educate their patients accordingly to ensure early diagnosis and management.

KEYWORDS

Canagliflozin; Empagliflozin; Euglycemia; Diabetes mellitus; Diabetic ketoacidosis; SGLT2 inhibitors; Sodium glucose cotransporter 2.

CORE TIP

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are a newer class of oral hypoglycemic drugs commonly prescribed for managing patients with diabetes mellitus (DM). Even though these drugs are effective in controlling blood glucose and have favourable cardiac effects, they may rarely lead to the development of euglycemic diabetic ketoacidosis (EDKA), which may complicate the disease course of these patients. Certain risk factors, like severe acute illness and major surgery, may predispose these patients to develop EDKA. The signs and symptoms of EDKA are similar to classic symptoms of diabetic ketoacidosis, but these patients have normal blood glucose levels, making the diagnosis difficult. Hence, a higher index of suspicion is warranted in such patients, as delay in diagnosis may lead to higher morbidity and mortality.

INTRODUCTION

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are relatively newer oral hypoglycemic agents (OHAs), which are increasingly being used to manage patients with diabetes mellitus (DM). The current American Diabetes Association (ADA) guidelines recommend using SGLT2i as one of the second-line agents, along with metformin, in managing of patients with type II diabetes mellitus (T2DM). They may also be used as the primary agent in patients with heart failure, chronic kidney disease, risk of atherosclerotic cardiovascular disease, and not tolerating metformin and those in whom metformin is contraindicated[1].

The mechanism of action of SGLT2i is independent of insulin secretion, making them an appealing agent for combination therapy. By inhibiting the SGLT2 receptors in the proximal tubules of the kidneys, it reduces glucose reabsorption and the renal threshold for glucose, thereby increasing renal excretion and reducing serum glucose levels[2].

SGLT2i has several clinical advantages, including reduced risk of hypoglycemic episodes, improved blood pressure control, reduction in weight and positive cardiovascular outcomes[2,3]. However, the use of SGLT2i is also associated with an increased incidence of genitourinary infections and hypovolemia[4]. Within months of FDA approval, cases of Diabetic Ketoacidosis (DKA) were reported using SGLT2i. In earlier reports, the incidence of DKA was 0.522 per 1,000 patient-years in patients taking canagliflozin 100 mg. A higher incidence of 0.763 per 1,000 patient-years was reported in patients taking higher doses of 300 mg. However, most patients had blood glucose levels higher than 300 mg/dl, and EDKA has been even more rarely reported[5].

DKA is a well-documented complication in patients with T1DM that is often recognized at the time of new diagnosis of diabetes and is generally precipitated by poor adherence to treatment or acute infection[6]. EDKA is a rare, but mostly missed and under-reported complication of DM management. It is arbitrarily defined as DKA without marked hyperglycemia. The ADA has defined EDKA as the presence of high anion-gap metabolic acidosis and increased plasma ketones in the presence of blood glucose levels below 250 mg/dl (13.9 mmol/L)[7].

The main aim of this meta-summary was to identify the predisposing factors, symptomatology, clinical course and outcomes of the patients on SGLT2i presenting with EDKA. This may aid the physicians involved in managing such patients to make an early diagnosis and prevent future events.

MATERIALS AND METHODS

For this metasummary, a systematic search for this review from PubMed, Science Direct, *Reference Citation Analysis* (RCA), and Google Scholar databases from January 1 2015, till January 31, 2023. The search terms used were "canagliflozin" OR "empagliflozin" OR "dapagliflozin" OR "SGLT2 inhibitors" OR "Sodium-glucose cotransporter 2" AND "euglycemia" OR "euglycemic diabetic ketoacidosis" OR

"metabolic acidosis". The inclusion criteria were (1) Case reports or case series with individual patient details and (2) Reported EDKA secondary to SGLT2i. Further, it was filtered for the literature published in English language and on adult (> 18 years) humans. We excluded 1) Conference abstracts; 2) Case reports or series which did not have individual biochemical data. The authors screened all the search results to include only the relevant literature. Duplicate articles from different search databases were excluded.

All the case reports, and case series were evaluated. The data were extracted for patient demographics, clinical symptomatology, clinical interventions, intensive care unit (ICU) course, need for organ support and outcomes. A datasheet for evaluation was further prepared.

Statistical analysis

The prepared datasheet was analyzed through Excel and Microsoft Office 2019. Categorical variables were presented as frequency and percentage. Mean [standard deviation (SD)] or median [interquartile range (IQR)] were used for describing the continuous variables. The statistical analyses were performed using SPSS (version 25.0, IBM SPSS Inc., Chicago, IL, USA). MS Office software (MS Office 2019, Microsoft Corp, WA, USA) was used for tabulation and final documentation.

RESULTS

The present review was done using PRISMA 2009 checklist (Figure 1). Ultimately, 108 case reports and 17 cases series with 169 unique patients meeting the predefined inclusion criteria were included (Appendix 1). The majority of included patients were from the United States of America (74, 43.8%) and Canada (23, 13.6%) (Figure 2). Most of the patients reported were females (54.4%, n = 92), and the commonly reported symptoms were gastrointestinal (nausea/vomiting 65.1%, abdominal pain 37.3%) and respiratory (breathlessness 30.8%). One hundred and forty-nine (88.2%) patients had underlying type I diabetes; the most commonly involved SGLT2i was empagliflozin, 46.8% (table 1). Most patients (78.7%) reported a triggering factor, the commonest

being acute severe infection (37.9%), which included patients with sepsis, COVID-19, other viral illnesses, and acute pancreatitis. The second common triggering factor was a perioperative period (24.3%), including bariatric surgery, coronary artery bypass grafting, orthopedic surgeries, pancreatectomy and cranial nervous system surgeries. Multiple triggering factors were reported in several patients (table 1). The median time on SGLT2i before developing EDKA was 30 days (interquartile range 6.5-165 days)

The median blood glucose level at presentation was 184.5 mg/dl. Most patients had severe metabolic acidosis with median serum pH of 7.14 and bicarbonate levels of 8.6 mmol/L. Hyperlactatemia was uncommon, with median lactate levels being 1.3 mmol/L (table 2). The overall mortality rate was only 2.4%.

DISCUSSION

In the present meta-summary, data from 169 individual case reports were analysed. Most patients (88.2%) were suffering from type II DM. Common presenting symptoms included nausea, vomiting, and abdominal pain. Empagliflozin was the commonest SGLT2i involved in 46.8% of cases. At presentation, the median blood glucose levels were 184.5 mg/dL, and the median blood pH was 7.14. Nearly 62% of patients were reported to require Intensive Care Unit (ICU) admission. Even though patients presented with severe metabolic acidosis, the overall mortality rate was only 2.4%.

DKA is a medical emergency which is diagnosed with hyperglycemia (blood glucose >250 mg/dl), metabolic acidosis (arterial pH <7.3, serum bicarbonate <15 mEq/l), and ketonemia. However, between 2.6% to 3.2% of DKA admissions may present with normal to near-normal blood glucose levels (blood glucose < 250 mg/dl)[8,9]. Even though the association of EDKA with SGLTi is well established, the cause for EDKA secondary to SGLT2i is not well recognized. Several mechanisms have been proposed, including independent action on pancreatic alpha cells, which increases plasma glucagon levels, stimulates hepatic ketogenesis, and reduces renal clearance of ketone bodies (especially beta-hydroxybutyrate and acetoacetate) [2,10]. SGLT2i increases renal excretion and blocks glucose reabsorption from the proximal convoluted tubule, thereby reducing serum glucose levels[11]. The combined effect of

these mechanisms may lead to ketonemia and ketoacidosis without much increase in serum glucose levels.

In the present meta-summary, most (88.2%) patients had type II diabetes. This could be explained by the fact that type II diabetes is much more common in adults accounting for almost 90% of cases[12]. Additionally, SGLT2 inhibitors are primarily recommended for treating type II diabetes. However, they are now being prescribed for type I diabetes, especially in those who failed to achieve glycemic targets with insulin alone, because their use is associated with improved HbA1C levels, reduction in body weight and better blood pressure control in these patients[14-16]. However, because of their increased potential to precipitate EDKA in TIDM, SGLT2i were generally discouraged in them[7,10,17].

A previous meta-summary analysing data from 77 patients with EDKA associated with SGLT2i also reported a higher incidence among females (67.5%) but reported canagliflozin (44.2%) as the commonest SGLT2 inhibitor involved. However, as our meta-summary shows, empagliflozin (46.8%) was the most commonly implicated agent, followed by canagliflozin (29.6%). This could be explained by the fact that canagliflozin was the first SGLT2 inhibitor commercially available; hence it was more widely prescribed earlier. With changing prescription practices, newer SGLT2i are more widely prescribed, explaining increased in reporting of side effects. Other findings of the previous meta-summary were similar to our findings, including the age of presentation (51.3 years), presenting symptoms and preponderance of type II diabetics (83.1%)[18]. The risk of developing EDKA is unrelated to the duration of exposure[18,19]. In the present study, the median duration of therapy with SGLT2i before the patients developed EDKA was 30 days, but patients developed EDKA even after one day or one dose of therapy[20,21].

The symptoms of EDKA are often non-specific and missed or ignored by patients and even their physicians due to misleadingly normal or near-normal blood glucose levels. This may lead them to maintain or reduce their insulin dose, further exacerbating ketosis and metabolic acidosis.

Testing for urinary ketone bodies remains a standard test for diagnosis of DKA. However, urine screening of ketones by nitroprusside agent only measures acetone and acetoacetate and does not detect beta-hydroxybutyrate, resulting in missing ketonuria. Hence, testing for blood

ketones (b-hydroxybutyrate) is generally recommended[7]. However, urinary ketones remained a standard test in the present meta-summary and were solely relied upon in 36.7% of cases.

Identifying precipitating factors can have significant clinical implications in preventing and managing EDKA. In the present study, acute infection and perioperative stress were found to be common triggering factors. Any major illness, trauma or surgery may result in a stress response associated with an increased release of catecholamines, heightened production of cortisol and reduced secretion and utilisation of insulin[22]. If patients continue their SGLT2i, reduced plasma glucose levels may mask the precise insulin requirements, increasing the risk of developing DKA.

As major surgery is an important factor that may precipitate EDKA, taking due precautions before surgery is imperative. Even the current recommendation by FDA and International Consensus Review on SGLT2i is to stop these drugs three days before surgery[23,24]. As these drugs are primarily excreted through the kidneys, it may be prudent to stop them even earlier in patients with deranged renal function[25].

Other common factors which may predispose patients to develop EDKA include prolonged fasting, low carbohydrate or ketogenic diet, excessive alcohol intake, dehydration and reduction in insulin dosage[18,19,26]. High protein and low carbohydrate diets may increase serum glucagon and reduce serum insulin levels. It may also cause an increase in counterregulatory hormones (epinephrine and cortisol), leading to increased free fatty acids and increased production of ketone bodies. As the reduction in insulin dosage may also precipitate DKA, stopping or drastically reducing the dose abruptly is not recommended. Moreover, the stress response of a systemic illness or major surgery is a common trigger; hence, timely discontinuation of SGLTi should be considered in acute stressful conditions like a major illness or post-operatively[27]. Patient education and pre-operative discontinuation of SGLTi and switching to insulin may aid in curtailing the risk of EDKA. Further, the European Medicines Agency suggests stopping SGLT2i immediately if symptoms or signs of DKA are suspected and not starting them until EDKA is excluded and an apparent precipitating factor has been identified and resolved[28].

Strength and limitations

The present meta-analysis compiled 125 global studies involving 169 unique patients who had developed EDKA secondary to SGLTi use. Additionally, we included only those studies which had individual patient details to compare patient demographics, precipitating factors and clinical outcomes. This is the largest such analysis, which adds strength to this review. However, the included studies were only case reports and case series which had no control arm. The studies were heterogeneous, and had a high risk of bias and missing data, which may affect the generalizability of the results. Additionally, because we did not include the case reports or series which did not report individual biochemical data, we may have missed some relevant reports.

CONCLUSIONS

Patients on SGLT2i may rarely develop EDKA, primarily due to certain predisposing factors, including severe acute infections and after major surgery. The signs and symptoms may be similar to DKA but with normal blood sugar levels, making diagnosis challenging. EDKA outcomes are good if recognized timely and corrective actions are taken. Hence, physicians managing such patients must be aware of this potential complication and educate patients accordingly to ensure early diagnosis and management.

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