Euglycemic diabetic ketoacidosis associated with SGLT2 inhibitors: A systematic review and quantitative analysis

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ABSTRACT

Background: Sodium-glucose cotransporter-2 inhibitors (SGLT2 inhibitors) rarely cause euglycemic diabetic ketoacidosis (euDKA) in diabetic patients. The aim was to identify demographic, clinical, and predisposing factors for euDKA from published case reports.

Methods: A systematic review of published case reports of euDKA in patients receiving SGLT2 inhibitors and meta-analysis of clinical trials to quantify the risk ratio (RR) of DKA in patients receiving SGLT2 inhibitors. PubMed and EMBASE databases were searched for the case reports of and clinical trials from January 2010 to August 2020. Studies published in English language were included and other languages were excluded. Data related to patients' demography, clinical presentation, drug and dose of SGLT2 inhibitors, and concomitant medication were extracted. Incidence of diabetic ketoacidosis (DKA) extracted from clinical trials. Data related to demographic, clinical, and other parameters presented as ratios and proportions and incidence of DKA in RR using Review Manager 5.3.

Results: Forty-seven of 160 reports with an aggregate of 77 patients were included in the analysis. The majority of the patients were females (67.53%), with T2DM and with gastrointestinal symptoms (58%). Surgery was the most common precipitating factor (n/N = 15/77). Canagliflozin (n/N = 34/77) was the commonest SGLT2 inhibitor reported along with metformin as the concomitant medication (63.6%). The pooled RR of DKA was 3.70 (95%CI 2.58, 5.29) and I² = 0%. Conclusion: euDKA is commonly seen in middle-aged female, T2DM patients taking SGLT2 inhibitors along with metformin. The risk of DKA in patients receiving SGLT2 inhibitors increases by 3.7 times than the other medication.

Keywords: Diabetes mellitus, DKA, euglycemic diabetic ketoacidosis, SGLT2 inhibitors

Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder associated with either deficiency of insulin called Type 1 diabetes mellitus (T1DM) or resistance to insulin action known as Type 2 diabetes mellitus (T2DM). T2DM is more common in adults and accounts for around 90% of all diabetes cases.[1] The sodium–glucose cotransporter 2 (SGLT2) inhibitors are one of the latest classes of antihyperglycemic medications and are currently highly recommended for the treatment of T2DM because of its multidimensional benefits on the cardiovascular system and renal system.[2,3] SGLT2 inhibitors (SGLT2i) act on the proximal tubular epithelium by inhibiting the reabsorption of glucose from the glomerular filtrate to the blood.[4] Glycosuria with SGLT2i usually results in a reduction of body weight and associated osmotic diuresis ends up in reducing the blood pressure; hence, they are quite beneficial in obese or overweight patients and hypertension with T2DM.[5] The cardiovascular benefits are due to the production of ketone bodies by SGLT2i, and its energy efficiency improves the cardiovascular benefits of empagliflozin are reported in “EMPA-REG Outcome trial,” which further makes these drugs a preferred choice for physicians. The cardiovascular benefits are due to the production of ketone bodies by SGLT2i, and its energy efficiency improves the cardiovascular benefits of empagliflozin are reported in “EMPA-REG Outcome trial,” which further makes these drugs a preferred choice for physicians. The cardiovascular benefits are due to the production of ketone bodies by SGLT2i, and its energy efficiency improves the cardiovascular benefits of empagliflozin are reported in “EMPA-REG Outcome trial,” which further makes these drugs a preferred choice for physicians. The cardiovascular benefits are due to the production of ketone bodies by SGLT2i, and its energy efficiency improves the cardiovascular benefits of empagliflozin are reported in “EMPA-REG Outcome trial,” which further makes these drugs a preferred choice for physicians. The cardiovascular benefits are due to the production of ketone bodies by SGLT2i, and its energy efficiency improves the cardiovascular benefits of empagliflozin are reported in “EMPA-REG Outcome trial,” which further makes these drugs a preferred choice for physicians. The cardiovascular benefits are due to the production of ketone bodies by SGLT2i, and its energy efficiency improves the cardiovascular benefits of empagliflozin are reported in “EMPA-REG Outcome trial,” which further makes these drugs a preferred choice for physicians. The cardiovascular benefits are due to the production of ketone bodies by SGLT2i, and its energy efficiency improves the cardiovascular benefits of empagliflozin are reported in “EMPA-REG Outcome trial,” which further makes these drugs a preferred choice for physicians. The cardiovascular benefits are due to the production of ketone bodies by SGLT2i, and its energy efficiency improves the cardiovascular benefits of empagliflozin are reported in “EMPA-REG Outcome trial,” which further makes these drugs a preferred choice for physicians. The cardiovascular benefits are due to the production of ketone bodies by SGLT2i, and its energy efficiency improves the cardiovascular benefits of empagliflozin are reported in “EMPA-REG Outcome trial,” which further makes these drugs a preferred choice for physicians. The cardiovascular benefits are due to the production of ketone bodies by SGLT2i, and its energy efficiency improves the cardiovascular benefits of empagliflozin are reported in “EMPA-REG Outcome trial,” which further makes these drugs a preferred choice for physicians. The cardiovascular benefits are due to the production of ketone bodies by SGLT2i, and its energy efficiency improves
cardiovascular and renal functions. With this evidence and insulin-independent mode of action, SGLT2i is a suitable class of drug for both T2DM and T1DM patients. In view of such a broad clinical utility of SGLT2i in diabetes, it is crucial to keep a track of their associated adverse events (AEs). Usually, these agents have a low tendency to cause hypoglycemia, still, because of glycosuria, there are chances of genital and urinary tract infections (UTI) and occasional orthostatic hypotension due to mild dehydration. In addition to the usual AEs, the US Food and Drug Administration (FDA) in May 2015, based on the 20 cases of diabetic ketoacidosis (DKA), published a warning with potential increased risk of DKA associated with the use of SGLT2i in both T2DM and T1DM patients. Later by June 2015, the European Medicines Agency also spotted 147 cases of DKA in patients on treatment with SGLT2i. Large trials like “DECLARE–TIMI 58 study” and “CREDENCE trial” have shown an increased probability of DKA with SGLT2i as compared to placebo. The cases of SGLT2i-associated DKA were atypical in presentation as the glucose levels were mildly elevated (<200 mg/dL), hence can be called euglycemic diabetic ketoacidosis (euDKA). The DKA is an emergency condition and is common in T1DM but is rare in T2DM. However, with the usage of SGLT2i in T2DM, the incidence of DKA is seen increasing. Being a life-threatening condition, early diagnosis and treatment are crucial for a better prognosis of the patient, but euglycemia in euDKA poses a great challenge in diagnosing the underlying DKA; hence, high clinical intuition is needed for diagnosis. Diabetes being a very prevalent noncommunicable disorder in the Indian population and with the evolution of SGLT-2 inhibitors in the therapy of DM, they are being currently used effectively and in the future might turn out to be a very commonly used drug by physicians. As the majority of the population in India lies in rural areas and inaccessibility of superspecialists physicians in the community, a major chunk of the diabetic patients is being treated by primary care and community physicians. Hence, it is crucial for them to have an idea of euDKA associated with SGLT2i, which will help to manage the cases in a better way. In this article, we systematically reviewed published case reports and case series of euDKA, to understand the demographic characteristics, clinical presentation, precipitating factors, and predisposed drug and its dose relationship with euDKA with SGLT2i.

Methods

This review was synthesized by following a prespecified study protocol (unpublished) and reported by following the guidelines of the “Preferred Reporting Items for Systematic Reviews and Meta-Analyses” statement. The prospective or retrospective descriptive case reports and case series of euDKA after treatment with SGLT2 inhibitors were included. The articles published in a language other than English and full text not available/accessible were excluded. Second, the clinical trials with SGLT2i were selected to assess the events of DKA in the drug group as compared to the placebo. All the potentially relevant articles were screened in two stages for the final eligibility. Initially, the abstracts of the selected articles were screened independently by two reviewers (TK, SD). Later, the full-text articles that met the inclusion criteria were extracted and independently reviewed.

Data extraction and synthesis

From the included case reports and case series, we extracted information like study characteristics, including author name, publication year, study type, number of patients, patient demographics (e.g., age and gender), details of SGLT2i (type and dose), and concomitant medicines. The events of DKA with the SGLT2i as compared to placebo were assessed from the included published clinical trials. The data was collated, disagreements were discussed, and differences were resolved between review authors. Grades of Recommendations, Assessment, Development, and Evaluations (GRADE) Pro GTD guidelines were used for grading the main outcome as per the GRADE recommendation. Online software was used for analysis. Observed data were combined with Review Manager 5 (RevMan) Version 5.3. (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Age is presented as mean and SD, sex, and ethnicity along with clinical presentation and precipitating factors presented in proportions. The incidence of DKA is summarized as a risk ratio (RR) with 95% CI. Heterogeneity was assessed based on the calculated I² (the proportion of total variability explained by heterogeneity), estimated using the restricted maximum likelihood-based method. We set predicated criteria for significant heterogeneity as $I^2 > 40\%$, and the analysis was done using a fixed-effect model even if heterogeneity is greater than 40% in the most pooled analysis, as heterogeneity was not taken care of by the random effect model. The reason for heterogeneity was assessed and explained and for high heterogeneity; inconsistency was downgraded for quality evidence in GRADE Pro analysis. To assess the publication bias, funnel plot assessment was applied.

Assessment of quality of evidence – GRADE pro analysis

The overall quality of evidence for each of the outcomes was assessed using GRADEpro GTD (guideline development tool) software based on the principles of GRADE. Risk of bias, the directness of evidence, consistency and precision of results, risk of publication bias, magnitude of the effect, dose-response
gradient, and influence of residual plausible confounding were assessed for grading the overall quality of evidence for individual outcomes. The final overall GRADE may be high, moderate, low, or very low. The online version of GRADE pro GDT software was accessed from the site: https://gradepro.org/120.

Ethical permission
The systematic review was synthesized from the data already published in open access and no direct contact with the patients was done; hence, ethical permission was not required.

Results
Our systematic search of the PubMed and EMBASE database resulted in an initial number of 160 potentially relevant articles. After removing seven duplicates, 153 articles were taken for the systematic review of 153 articles, 45 were review, 16 were communications, 19 were conference abstracts, 8 were research articles, 4 were book chapters, and five articles were not accessible hence excluded.

Applying the inclusion/exclusion criteria on 52 full-text documents, five other language articles were excluded. Finally, 47 articles were included for the synthesis of this review. In 42 case reports and 5 case series, we got 77 patients with a mean age of 51.31 years (SD = 15.25). Basic characteristics of individual case reports and case series of euDKA with SGLT-2i are summarized in Table 1. The majority of the patients reported were females (67.5%, n = 52). The majority of the reports did not mention (n/N = 62/77) the ethnicity still among mentioned, Asians (46.6%, n = 7) was the most common. Among the disease distribution, T2DM was most prevalent, followed by T2DM with cardiovascular diseases like hypertension, coronary artery diseases, arrhythmia, etc., T1DM, T2DM with oncological disorders like benign or malignant cancers, T2DM with other endocrine disorders like hypothyroidism, etc., T2DM with renal dysfunction like acute or chronic kidney disease, etc., T2DM with multiple sclerosis, T1DM with other endocrine disorders like hypothyroidism, etc., and others which include multiple diseases and comorbidities [Table 2].

The presenting complaints were mentioned in 45 of 77 patients of all the case reports. The commonest presenting complaints of euDKA (58%, n = 45) were nausea, vomiting, abdominal pain, malaise, and sometimes shortness of breath. The prevalent precipitating factor for DKA was surgery as about 33% of patients developed DKA in their postsurgical period. Other precipitating factors of DKA were associated with UTI, cardiovascular irregularities, acute gastroenteritis, etc.

Canagliflozin (44%, n = 34) was the commonest SGLT-2i reported in the selected studies followed by Dapagliflozin (27%, n = 21) and Empagliflozin (25%, n = 19). A dose-dependent increase in the number of cases of DKA was observed with all the three SGLT2i [Figure 2]. Among the concomitant medications used along with SGLT2i, metformin was the commonest, followed by Insulin, Dipeptidyl peptidase-4 (DPP-4) i, sulfonylureas along with vitamin B12, vitamin C, vitamin D, and multivitamins [Table 3].

Figure 1: PRISMA flow chart depicting the study selection process
| Author/Year | Age/Gender | Drug and Dose | Disease distribution | Presenting complaints |
|-------------|------------|---------------|----------------------|-----------------------|
| Adachi J et al., 2017<sup>59</sup> | 27 y, F | Canagliflozin 300 mg/day | T2DM | DKA |
| Alhassan S et al., 2018<sup>60</sup> | Case 1: 73 y, F, Case 2: 70 y, M, Case 3: 69 y, F | Empagliflozin 25 mg daily, Canagliflozin 300 mg daily, Canagliflozin100 mg | T2DM, T2DM and hypertension | Case 1: nausea, vomiting, DKA, Case 2: Spinal stenosis was admitted for elective C3-C7 spinal fusion, Case 3: Admitted with ST elevation myocardial infarction (STEMI) |
| Allison R et al., 2019<sup>61</sup> | 47 y, M | Empagliflozin | Multiple Sclerosis with T2DM | Generalized weakness, known case of multiple sclerosis (MS) diagnosed 4 years ago |
| Andrews TJ et al., 2017<sup>62</sup> | 57 y, F | Empagliflozin | T2DM, hypothyroidism, Hepatitis B, chronic obstructive pulmonary disease, coronary artery disease, myocardial infarction, pulmonary hypertension, depression, vitamin D deficiency, and restless leg syndrome | Progressive altered mental status for the past 2 days |
| Bader N et al., 2016<sup>63</sup> | 27 y, F | Canagliflozin | T1DM, depression, hypothyroidism | DKA |
| Badwal K et al., 2018<sup>64</sup> | 25 y, M | Dapagliflozin | T2DM with acute pancreatitis | One-day history of abdominal pain, nausea, and emesis |
| Bennoussa JA et al., 2016<sup>65</sup> | 39 y, F, Caucasian | Canagliflozin | T2DM with hypothyroidism | Nausea, Vomiting, anorexia, abdominal pain and myalgia |
| Brown F et al., 2018<sup>66</sup> | 53 y, M | Dapagliflozin | T2DM, Roux-En-Y Gastric bypass surgery 6 weeks prior, hypertension and hypercholesterolemia | One week history of nausea, vomiting, anorexia, and generalized abdominal pain |
| Bteich F et al., 2019<sup>67</sup> | 58 y, F | Empagliflozin 25 mg daily | T2DM with essential hypertension and obstructive sleep apnea | Altered mental status |
| Candelario N et al., 2017<sup>68</sup> | 61 y, F | Empagliflozin | T2DM with diet-controlled hypertension | Right upper quadrant abdominal pain for a day |
| Chao HY et al., 2020<sup>69</sup> | Case 1: 40 y, M, Case 2: 60 y, M | Case 1: Empagliflozin, Case 2: Dapagliflozin | Case 1: T2DM with alcoholic liver cirrhosis, Case 2: T2DM with alcoholic liver cirrhosis | Case 1: Nausea, fatigue, and dyspnea, Case 2: Severe dyspnea and nausea |
| Chou YM et al., 2018<sup>70</sup> | 61 y, F | Dapagliflozin 10 mg OD | T2DM | Body weakness, dyspnea, nausea, vomiting, and mild abdominal pain for the past 2 days |
| Clement M et al., 2016<sup>71</sup> | 42 y, F | Canagliflozin 100 mg | T2DM, hypertension, obesity, psoriasis, hypothyroidism, and polycystic ovary syndrome | Shortness of breath |
| Dai Z et al., 2016<sup>72</sup> | 49 y, M | SGLT 2 inhibitors | T2DM and vasospastic angina | Suddenly lost consciousness while sightseeing, shortly after he complained of nausea |
| Diaz-Ramos A et al., 2019<sup>73</sup> | 44 y, F | Canagliflozin 100 mg daily | T2DM | Generalized weakness for 3 days |

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Table 1: Contd...

| Author/Year          | Age/Gender | Drug and Dose | Disease distribution                      | Presenting complaints                                                                 |
|----------------------|------------|---------------|-------------------------------------------|----------------------------------------------------------------------------------------|
| Dizon S et al., 2017 | 55 y, F    | Canagliflozin 300 mg daily | T2DM, Roux-en-Y gastric bypass surgery | Case 1: Roux-en-Y gastric bypass surgery, On POD #17, she developed nausea, vomiting, low-back pain, and dysphagia |
|                      | 38 y, F    | Canagliflozin 300 mg daily | T2DM, Roux-en-Y gastric bypass surgery | Case 2: Roux-en-Y gastric bypass surgery, 7 days after starting canagliflozin, she presented with nausea, vomiting, dizziness, and dehydration |
|                      | 45 y, M    | Canagliflozin 300 mg daily | T2DM                                      | Case 3: Three-day history of shortness of breath and was found to have a mixed metabolic acidosis |
|                      | 51 y, F    | Canagliflozin 300 mg daily | T2DM, laparoscopic cholecystectomy        | Case 4: Severe ketoacidosis                                                              |
|                      | 29 y, F    | Canagliflozin 300 mg daily | T2DM                                      | Case 5: Nausea, vomiting and shortness of breath                                          |
|                      | 54 y, M    | Canagliflozin 300 mg daily | T2DM                                      | Case 6: Two months after starting canagliflozin, he had a laparoscopic cholecystectomy. On POD #1, he experienced shortness of breath and was found to have a pulmonary embolus |
|                      | 67 y, F    | Canagliflozin 300 mg daily | T2DM                                      | Case 7: Presented with severe ketoacidosis                                               |
|                      | 74 y, M    | Canagliflozin 300 mg daily | T2DM                                      | Case 8: Cholecystitis, biliary sepsis, and ketoacidosis                                  |
|                      | 74 y, F    | Canagliflozin 300 mg daily | T2DM, operative repair of an intertrochanteric fracture | Case 9: Polydipsia, dizziness and loss of appetite                                       |
|                      | 10-74 y, F | Canagliflozin 100 mg daily | T2DM                                      | Case 10: Admitted to hospital for operative repair of an intertrochanteric fracture. On POD #1, she restarted on all her oral diabetes medications On POD #5, she felt weak, confused, and generally unwell |
| Dull RB et al., 2017 | 55 y, F    | Dapagliflozin 10 mg OD | T2DM, hyperlipidemia, hypothyroidism, and anemia | Dizziness and shortness of breath worsening over 1 week                                 |
|                      | 62 y, M    | Empagliflozin 25 mg OD | T2DM, past medical history of heart failure with preserved ejection fraction, cerebrovascular accident, coronary artery disease, hypertension, hyperlipidemia, obstructive sleep apnea, morbid obesity, and neuropathy | Sudden-onset abdominal pain and multiple episodes of nonbloody vomitus during the previous 24 h |
| Earle M et al., 2020 | 31 y, F    | Canagliflozin | T2DM                                      | Malaise, nausea, and abdominal pain                                                      |
| Ghosh MSA, 2019      | 52 y, M    | Empagliflozin | T2DM                                      | Weakness, poor oral intake, malaise, and tightness of chest in the evening                |
| Iqbal I et al., 2019  | 75 y, F    | Dapagliflozin | T2DM, hypertension, chronic kidney disease stage III | Altered mental status and confusion                                                      |
| Jazi M et al., 2016   | 51 y, M    | Canagliflozin | T2DM and Hypertension                     | Malaise, cough, and intermittent shortness of breath                                    |
| Karakaya Z et al., 2018 | 72 y, F    | Dapagliflozin | T2DM                                      | Altered mental status two days after her hip prosthesis operation                       |
| Kelmenson DA et al., 2017 | 50 y, F    | Canagliflozin 300 mg daily | T2DM                                      | Four days of nausea, vomiting, abdominal pain, and decreased oral intake                |
| Koch RA et al., 2018  | 61 y, F    | Dapagliflozin | T2DM                                      | Profound acidemia and ketonemia.                                                        |

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Table 1: Contd...

| Author/Year                      | Age/Gender | Drug and Dose | Disease distribution | Presenting complaints |
|----------------------------------|------------|---------------|----------------------|-----------------------|
| Kum-Nji JS et al., 2017          | Case 1: 48 y, M | Case 1: Canagliflozin 300 mg daily | T2DM                 | Case 1: Abdominal pain |
|                                 | Case 2: 62 y, F | Case 2: Canagliflozin 100 mg daily | T2DM, metastatic pancreatic adenocarcinoma | Case 2: Abdominal pain revealed metastatic pancreatic adenocarcinoma |
|                                 | Case 3: 37 y, F | Case 3: Dapagliflozin 10 mg daily | T2DM                 | Case 3: Nausea, vomiting, and weakness |
|                                 | Case 4: 52 y, F | Case 4: Dapagliflozin 5 mg daily | T2DM                 | Case 4: Generalized weakness, malaise, polydipsia, and polyphagia |
|                                 |             |               |                      |                       |
| Lane S et al., 2018              | Case 1: 54 y, M | Case 1: Canagliflozin 300 mg daily | T2DM, hypercholesterolemia, and gastrointestinal reflux | Presented for bariatric surgery with a body mass index of 40.1 kg/m2 |
|                                 | Case 2: 58 y, M | Case 2: Empagliflozin 25 mg daily | T2DM, DKA followed by cardiopulmonary bypass (CPB) | Case 1: Elective CABG |
|                                 | Case 3: 54 y, M | Case 3: Empagliflozin 25 mg daily | T2DM, DKA followed by coronary artery bypass grafting (CABG) | Case 2: Elective CABG |
|                                 |             |               |                      | Case 3: Elective off-pump CABG (OPCAB) |
|                                 |             |               |                      |                       |
| Lau A et al., 2017               | Case 1: 54 y, M | Case 1: Canagliflozin 300 mg daily | T2DM                 | Case 1: Elective CABG |
|                                 | Case 2: 58 y, M | Case 2: Empagliflozin 25 mg daily | T2DM                 | Case 2: Elective CABG |
|                                 | Case 3: 54 y, M | Case 3: Empagliflozin 25 mg daily | T2DM                 | Case 3: Elective off-pump CABG (OPCAB) |
|                                 |             |               |                      |                       |
| Lee IH et al., 2020              | Case 1: 76 y, F | Case 1: Dapagliflozin 10 mg/ day | T2DM                 | General weakness, fever, oliguria, nausea, and vomiting |
|                                 |             |               |                      | Total knee replacement |
| Levine JA et al., 2017           | Case 1: 60 y, M | Canagliflozin 300 mg daily | T2DM, coronary artery disease, arthritis | Acute gastroenteritis with nausea and abdominal pain |
|                                 |             |               |                      | Case 1: Vomiting and abdominal pain |
|                                 |             |               |                      | Case 2: Abdominal pain, diarrhea, and fever |
|                                 |             |               |                      | Case 3: Passing liquid stools, together with emesis |
| Lin YH, 2018                    | Case 1: 22 y, F | Case 1: none | T2DM, history of DKA, hypothyroidism | Case 1: Vomiting and abdominal pain |
|                                 | Case 2: 50 y, F | Case 2: Dapagliflozin 10 mg/day | T2DM, hypertension, dyslipidemia, left-side breast cancer | Case 2: Abdominal pain, diarrhea, and fever |
|                                 | Case 3: 74 y, M | Case 3: Dapagliflozin 10 mg/day | T2DM, CKD, Cryptogenic Liver Cirrhosis | Case 3: Passing liquid stools, together with emesis |
|                                 |             |               |                      |                       |
| Lucero P et al., 2018            | Case 1: 68 y, F | Empagliflozin 10 mg once daily | T2DM, left temporal meningioma | Left temporal meningioma |
|                                 | Case 2: 67 y, F | Empagliflozin 25 mg/day | T2DM                 | Abdominal pain and impaired conscious level (Glasgow Coma Scale: 12), occurring after 1 week of fever, malaise, and dyspnea |
|                                 | Case 3: 74 y, M | Dapagliflozin 25 mg/day | T2DM, pancreatic adenocarcinoma | Case 1: Incidental finding of a body of pancreas mass on magnetic resonance imaging for follow-up of a stable ovarian cyst |
|                                 |             | Dapagliflozin 10 mg/day | T2DM, pancreatic adenocarcinoma | Case 2: Obstructive jaundice and elevated liver function tests |
|                                 |             |               |                      |                       |
| Mackintosh C et al., 2019       | Case 1: 64 y, M | Case 1: Canagliflozin 300 mg daily | T2DM, HTN             | Nausea, vomiting, and abdominal pain |
|                                 | Case 2: 67 y, F | Case 2: Dapagliflozin 10 mg/day | T2DM                 | Metallic taste in mouth, thick saliva, and malaise |
|                                 | Case 3: 74 y, M | Case 3: Dapagliflozin 10 mg/day | T2DM                 | Case 1: Tachypnea and tachycardia |
|                                 | Case 4: 77 y, F | Canagliflozin 10 mg/day | T2DM                 | Case 2: Elective sigmoid colectomy |
|                                 |             |               |                      | Case 3: Upper respiratory tract infection (URI) |
|                                 | Case 5: 82 y, F | Canagliflozin 10 mg/day | T2DM                 | Case 4: Vomiting and had a reduction in consciousness. She was admitted for eDKA |
|                                 | Case 6: 84 y, F | Canagliflozin 10 mg/day | T2DM                 | Case 5: Presumed euglycemic ketosis, severe headache, and nausea not relieved with her migraine medications |
|                                 |             |               |                      | Case 6: Nausea and vomiting several hours after eating in a restaurant |
|                                 |             |               |                      | Case 7: Nausea and vomiting presented in the hospital |
|                                 |             |               |                      | Case 8: eDKA |
|                                 |             |               |                      | Case 9: Elective bilateral cervical foraminotomy. Ten days of constipation and fatigue |
|                                 |             |               |                      |                       |
| Pujara S et al., 2017            | Case 1: 39 y, M | Case 1: Canagliflozin 300 mg daily | T2DM, HTN             | Nausea, vomiting, and abdominal pain |
|                                 | Case 2: 50 y, F | Case 2: Dapagliflozin 10 mg/day | T2DM                 | Metallic taste in mouth, thick saliva, and malaise |
|                                 |             |               |                      | Case 1: Tachypnea and tachycardia |
|                                 |             |               |                      | Case 2: Elective sigmoid colectomy |
|                                 |             |               |                      | Case 3: Upper respiratory tract infection (URI) |
|                                 |             |               |                      | Case 4: Vomiting and had a reduction in consciousness. She was admitted for eDKA |
|                                 |             |               |                      | Case 5: Presumed euglycemic ketosis, severe headache, and nausea not relieved with her migraine medications |
|                                 |             |               |                      | Case 6: Nausea and vomiting several hours after eating in a restaurant |
|                                 |             |               |                      | Case 7: Nausea and vomiting presented to the hospital |
|                                 |             |               |                      | Case 8: eDKA |
|                                 |             |               |                      | Case 9: Elective bilateral cervical foraminotomy. Ten days of constipation and fatigue |

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**Table 1: Contd...**

| Author/Year          | Age/Gender | Drug and Dose                      | Disease distribution                  | Presenting complaints                                                                 |
|----------------------|------------|------------------------------------|---------------------------------------|---------------------------------------------------------------------------------------|
| Rafey MF et al., 2019 | Case 1: 44 y, M<br>Case 2: 59 y, F | Case 1: Canagliflozin 300 mg once daily<br>Case 2: Empagliflozin 25 mg once daily | T2DM<br>T2DM, renal oncocytoma        | Case 1: Generalized weakness, lethargy, nausea, and anorexia, Six days post C5-C7 cervical decompression<br>Case 2: Generalized weakness, dyspnea, and presyncope 3 days after elective laparoscopic right partial nephrectomy for removal of a renal oncocytoma |
| Sampani E i., 2020   | 51 y, F    | Empagliflozin 25 mg once a day     | T2DM, peptic ulcer, uterine fibroids | Weakness, tachypnea, anorexia, vomiting, and mild abdominal pain                      |
| Wang AY et al., 2017 | 61 y, F    | Empagliflozin 25 mg per day        | T2DM                                  | Severe vomiting for 1 day                                                             |
| Wang KM et al., 2020 | 40 y, F    | Empagliflozin                      | T2DM                                  | Scheduled cerebral revascularization for moyamoya disease                              |
| Yamamoto M et al.,   | 51 y, M    | Empagliflozin                      | T2DM                                  | Nausea and vomiting                                                                    |
| Yeo SM et al., 2019   | 23 y, F    | Dapagliflozin 10 mg once a day     | T2DM, acute pancreatitis due to hypertriglyceridemia | Severe abdominal pain                                                                  |
| Zhang L et al., 2018  | 70 y, M    | Empagliflozin                      | T2DM, paroxysmal atrial fibrillation, and dyslipidemia | Nausea, vomiting, and generalized weakness                                              |

**Table 2: Patients characteristics of included case reports for euglycemic diabetic ketoacidosis**

| Characteristics                        | Characteristics | n/N (%) |
|----------------------------------------|-----------------|---------|
| Sociodemographic features              | Gender          | Male    | 25/77 (32.47) |
|                                        |                 | Female  | 52/77 (67.53) |
|                                        | Ethnic Distribution | Asian | 7/77 (9) |
|                                        |                 | Caucasian | 4/77 (5.2) |
|                                        |                 | White Irish | 2/77 (2.6) |
|                                        |                 | African American | 1/77 (1.3) |
|                                        |                 | Hispanic | 1/77 (1.3) |
|                                        |                 | Not mentioned | 62/77 (80.5) |
| Disease distribution                   | T2DM            | Without any comorbidities | 37/77 (48.20) |
|                                        |                 | With multiple Sclerosis | 1/77 (1.30) |
|                                        |                 | With cardiovascular diseases | 14/77 (18.00) |
|                                        |                 | With renal disease | 2/77 (2.60) |
|                                        |                 | With oncological disorder | 6/77 (7.80) |
|                                        |                 | With endocrine disorders | 4/77 (5.20) |
|                                        | T1DM            | Without any comorbidities | 9/77 (11.60) |
|                                        |                 | Endocrine disorders | 1/77 (1.30) |
| Drug distribution                      | Others (Multiple diseases and comorbidities ) | 3/77 (3.90) |
|                                        | Concomitant medications along with SGLT2 inhibitors | SGLT2i + Metformin | 49/77 (63.63) |
|                                        |                 | SGLT2i + Insulin | 48/77 (62.33) |
|                                        |                 | SGLT2i + Dipeptidyl peptidase-4 inhibitors | 16/77 (20.77) |
|                                        |                 | SGLT2i + Sulfonylureas | 14/77 (18.18) |
|                                        |                 | SGLT2i + Liraglutide or Dulaglutide | 5/77 (6.5%) |
|                                        |                 | SGLT2i + Pioglitazone or Rosiglitazone | 2/77 (2.6%) |

Incidence of DKA from the previously published clinical trials

Sixteen studies comprising a total of 31,256 patients (18,956 in the SGLT2i group and 12,300 in the placebo group) were included for pooling the RR for DKA. The pooled RR was 3.70 (95% CI 2.58, 5.29), I² was 0% and the test overall effect was significant (P < 0.00001) [Figure 3]. High-quality evidence as per GRADE Pro analysis is shown in Table 3. Publication bias was low as the funnel plot of 16 studies is symmetrical around the effect estimate [Figure 4].

**RISK OF BIAS: RoB-2**

The overall risk of bias was recorded as low in all the included studies. The weighted summary plot of ROB is shown in [Figure 5].

**Discussion**

SGLT2 inhibitors are emerging as a preferred drug because of its effectiveness in decreasing glycated hemoglobin levels along with weight loss, increasing peripheral insulin sensitivity, and
preventing cardiovascular comorbidities in diabetic patients.\[^{[83]}\]

In addition, SGLT2i have a potentially beneficial role in decreasing morbidity and mortality in patients with congestive heart failure.\[^{[77]}\]

There are two different classes of SGLT transporters in the proximal convoluted tubule of the nephron, classified as SGLT-1 and SGLT-2. SGLT-2 itself reabsorbs nearly 90% of total filtered glucose into the nephron. SGLT2i decreases the renal threshold drastically, causes osmotic diuresis, and reduces plasma glucose concentration.\[^{[84]}\]

Blau et al.\[^{[85]}\] observed that the risk of DKA is seven times more in diabetic patients taking the SGLT2i than the patient taking DPP-4 inhibitors. Though reported by Blau et al., the incidence of euDKA still not clear maybe because of its rare occurrence, underreporting as well as due to underdiagnosis.\[^{[51-85]}\]

The reason for euDKA and precipitating factors in DM patients still needs comprehensive research.

Recent FDA warning about euDKA associated with SGLT2i raised concern to understand the patient profile and presentation symptoms for risk evaluation in patients taking SGLT2i.\[^{[7]}\]

In this review, we studied patient demographic characteristics, clinical presentation, precipitating factors, and predisposed drug and its dose, from the published reports to enable treating physicians for early diagnosis and treatment of euDKA and prevent the potential adverse outcome.

### Clinical presentation

In this review, we observed that half of the patients had T2DM without any comorbidities and about 1 in 5 patients had T2DM with cardiovascular disease, and 1 in 10 patients had T1DM. The majority of patients were middle age diabetic females (66%), maybe because of lower body mass index and poor glycogen stores.\[^{[51]}\]

The clinical presentation in these patients is similar to traditional symptoms of DKA, which include nausea, vomiting, abdominal pain, shortness of breath, etc. We also observed that diabetic patients during the postoperative period or patients with cardiovascular comorbidities prone to euDKA. This observation helps clinicians or treating physicians to create awareness among patients and healthcare providers about the risk of euDKA.

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**Figure 2:** Dose-dependent number of euDKA cases reported in the literature

| Study or Subgroup | SGLT 2 Inhibitors | Control | Risk Ratio |
|-------------------|-------------------|---------|------------|
|                   | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| 1.1.1 Certain DKA |        |       |       |       |        |                      |                      |
| Binder T et al., 2017 | 0      | 11    | 0      | 10    | Not estimable |                      |                      |
| Buse JB et al., 2018 | 20     | 525   | 1      | 288   | 3.0%    | 10.21 [1.38, 75.68] |                      |
| Dandona P et al., 2018 | 52     | 573   | 9      | 280   | 28.1%   | 2.02 [1.31, 5.24]  |                      |
| Danne T et al., 2018 | 15     | 524   | 0      | 258   | 1.5%    | 15.29 [9.92, 254.59] |                      |
| Henry et al., 2015, dapagliflozin | 0      | 7      | 0      | 13    | Not estimable |                      |                      |
| Henry RF et al., 2015, canagliflozin | 12     | 234   | 0      | 117   | 1.5%    | 2.55 [0.73, 9.19]  |                      |
| Kawamori R et al., 2018 | 12     | 364   | 1      | 196   | 3.0%    | 6.13 [0.80, 46.80] |                      |
| Kudiyas ND et al., 2016 | 2      | 17    | 0      | 9     | 1.5%    | 2.79 [0.15, 52.35] |                      |
| Mathieu C et al., 2018 | 13     | 541   | 0      | 272   | 1.5%    | 13.60 [0.61, 227.91] |                      |
| McEllern J et al., 2019 | 3      | 2368  | 0      | 2371  | 1.1%    | 7.01 [0.36, 135.61] |                      |
| Meher M et al., 2018 | 0      | 6     | 0      | 6     | Not estimable |                      |                      |
| Neal B et al., 2017 | 3      | 5795  | 1      | 4347  | 2.0%    | 2.25 [0.23, 21.63] |                      |
| Peters AJ et al., 2016 | 17     | 234   | 0      | 117   | 1.5%    | 17.57 [1.07, 289.70] |                      |
| Rosenson J et al., 2018 | 39     | 1221  | 9      | 725   | 25.6%   | 2.57 [1.25, 5.28]  |                      |
| Shimada A et al., 2018 | 0      | 37    | 0      | 11    | Not estimable |                      |                      |
| Zimman et al., 2015 | 4      | 4687  | 1      | 2333  | 3.0%    | 1.99 [0.22, 17.80] |                      |
| Subtotal (95% CI) | 17194  | 11303 | 74.0% | 4.68 [2.79, 6.17] |

Total events: 192

Heterogeneity: $I^2 = 8.18, df = 11 (P = 0.70); P = 0$

Test for overall effect: $Z = 6.06 (P = 0.00001)$

1.1.2 Possible or Potential DKA

| Study or Subgroup | SGLT 2 Inhibitors | Control | Risk Ratio |
|-------------------|-------------------|---------|------------|
|                   | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| Mathieu C et al., 2018 | 10     | 541   | 2      | 272   | 6.0%    | 2.51 [0.55, 11.39] |                      |
| Rosenson J et al., 2018 | 31     | 1221  | 7      | 725   | 19.0%   | 2.63 [1.18, 5.94]  |                      |
| Subtotal (95% CI) | 1762  | 997   | 26.0% | 2.60 [1.27, 5.33] |

Total events: 47

Heterogeneity: $I^2 = 0.00, df = 1 (P = 0.96); P = 0$

Test for overall effect: $Z = 2.61 (P = 0.009)$

1.1.3 Total DKA

| Study or Subgroup | SGLT 2 Inhibitors | Control | Risk Ratio |
|-------------------|-------------------|---------|------------|
|                   | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| Mathieu C et al., 2018 | 10     | 541   | 2      | 272   | 6.0%    | 2.51 [0.55, 11.39] |                      |
| Rosenson J et al., 2018 | 31     | 1221  | 7      | 725   | 19.0%   | 2.63 [1.18, 5.94]  |                      |
| Subtotal (95% CI) | 1762  | 997   | 26.0% | 2.60 [1.27, 5.33] |

Total events: 233

Heterogeneity: $I^2 = 8.40, df = 13 (P = 0.01); P = 0$

Test for overall effect: $Z = 7.16 (P = 0.00001)$

Test for subgroup differences: $I^2 = 11.3, df = 1 (P = 0.29); P = 0.116$

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**Figure 3:** Incidence of DKA reported in randomized clinical trials in patients taking SGLT2 inhibitors versus control in diabetes patients
Table 3: GRADE recommendation for diabetes ketoacidosis for use of SGLT-2 inhibitors in DM patients

| No of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Adverse events comparison in SGLT2 inhibitor vs. Placebo group | Relative (95% CI) | Absolute (95% CI) | Certainty | Importance |
|---------------|--------------|--------------|---------------|--------------|-------------|---------------------|---------------------------------------------------------------|-------------------|-----------------|-----------|------------|
| Events of DKA in SGLT2 inhibitors vs. Placebo - Certain DKA | 16 RCT | not serious a | not serious | not serious b | strong association c | | 233/18956 (1.2%) | 31/12300 | (0.3%) | RR 3.70 | 7 more per 1,000 (from 4 more to 11 more) |
| Events of DKA in SGLT2 inhibitors vs. Placebo - Possible or Potential DKA | 2 RCT | not serious a | not serious | not serious b | strong association c | | 192/17194 (1.1%) | 22/11303 | (0.2%) | RR 4.08 | 6 more per 1,000 (from 3 more to 10 more) |

CI: Confidence interval; RR: Risk ratio; RCT: Randomized Clinical Trials Explanations. a: I²=0%, hence low heterogeneity. b: CI does not include one and overall information size is adequate; therefore, the outcome is precise. c: RR is greater than 2, it is regarded as large effect.
higher in T2DM patients and 5 to 12-fold in T1DM patients as reported in FDA adverse event reporting system (FAERS). In FAERS data, out of all DKA case reports, euDKA was reported in 71% of cases.

The current pandemic of COVID-19 has infected a large population around the world and people with comorbidities like DM are more prone to develop a severe form of the disease. Recently, the cases of euDKA have also been seen in the COVID-19 patients and the probability might increase in COVID-19 because of the viral infection and its associated complications. Vitale et al. (2018) in their case series also reported cases of T2DM with no previous history of DKA and on SGLT-2 inhibitors presented with euDKA.

Mechanism

The pathophysiology of euDKA in patients receiving SGLT2 inhibitors remains unclear, but there are multiple hypotheses explained to understand the mechanism of euDKA. The most popular hypothesis was that SGLT2 inhibitors increase glucagon secretion by binding to alpha cells of pancreatic islets and causing gluconeogenesis. Simultaneously, it decreases in blood glucose by hastening its renal excretion from the plasma. A decrease in blood glucose cause decreased insulin secretion from islets which results in excess ketone body formation. In addition to the above mechanism, it was observed that in type 1 diabetic patients, the decreased daily requirement of insulin causes increased lipolysis in adipose tissue and increased ketone body synthesis in the liver. In addition, increased reabsorption of ketone bodies from the kidney due to positive electrochemical gradient generation by inhibition of SGLT2 transporter. Bonner C et al. (2019) observed that treatment with dapagliflozin in mice resulted in inhibition of Solute Carrier Family 5 (Sodium/Glucose Cotransporter), Member 2 (SLC5A2) on pancreatic alpha cells thereby increasing glucagon. Also, increased glucagon gene expression results in increased glucagon synthesis leading to increased hepatic gluconeogenesis and excess fatty acid degradation leading to excess production of ketone bodies.

Strengths and Limitations

We did a comprehensive systematic review describing the data on demographic, clinical characteristics of euDKA in patients taking SGLT2 inhibitors and the dose–dependent relationship between euDKA and SGLT2 inhibitors. There are chances of missing out on case reports published in local languages as we included only case reports published in the English language. We analyzed symptomatic reported cases. Case reports are good for generating hypotheses, but the potential risk of bias due to lack of external validity cannot be ruled out.

GRADE Conclusion

The overall quality of the systematic review is high as the incidence of DKA has a high quality of evidence. This evidence suggests that further research is very unlikely to have an important impact on our confidence in the estimate and change the estimate.

Key points and Summary

- DM is a prevalent noncommunicable disease in India.
- SGLT-2 inhibitor is a crucial class of novel antidiabetic drugs in view of their additive cardiovascular benefits.
- euDKA in case of diabetic ketoacidosis without hyperglycemia and is rarely seen with use with SGLT-2 inhibitors.
- Type-2 DM patients with a long history and inadequate control of blood glucose seem to be more prone to develop euDKA.
- The cause of euDKA with SGLT-2 inhibitors might be an increase in glucagon secretion, excess ketone body formation, and increased reabsorption of ketone bodies from the kidney.
- The symptoms of euDKA are lesser as compared to classical DKA; therefore, early detection of this potential complication might be a challenging task.
- Physicians treating diabetic patients with SGLT-2 inhibitors should have a high level of suspicion to diagnose the condition early and treat it as normal glucose levels in these patients mask the diagnosis of DKA.

Conclusion

Systematic review of euDKA and the incidence of DKA with SGLT-2 inhibitors were performed, to assist the endocrinologists and primary care physicians in getting aware of these complications. This helps in the prevention, early diagnosis, and
treatment of complications. With the increasing use of SGLT2 inhibitors, there is a likelihood of an increase in the number of euDKA cases with this group of drugs. Hence, it is important to identify patient characteristics and precipitating factors to prevent similar cases in the future. We need multicentric dedicated studies for the evaluation of risk factors of SGLT2 inhibitor-induced euDKA and associated biomarkers including pharmacogenomics of siRNA of SCL5A2 gene.

Author's contribution
Study design and planning of systematic review – All of the authors.
Literature search – TK, SD, and SBV
Figures – SBV, SS, and SD
Tables – SBV, SA, and TK
Data collection and analysis – SD, TK, and SBV
ROB – SBV, SD, and SA
GRADE analysis – SS, SBV, and query resolved by all authors
Data interpretation – SD, SBV, SS, and SA
Writing – All authors
Corrections and final approval of manuscript – All of the authors

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