Original Article

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 I^2 = 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 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

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cardiovascular and renal functions.[6,7] With this evidence and insulin-independent mode of action, SGLT2i is a suitable class of drug for both T2DM and T1DM patients.[8,9] 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.[10] 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.[11] Later by June 2015, the European Medicines Agency also spotted 147 cases of DKA in patients on treatment with SGLT2i.[12] Large trials like "DECLARE–TIMI 58 study" and "CREDENCE trial" have shown an increased probability of DKA with SGLT2i as compared to placebo.[13,14] 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).[10,15,16] 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.[10,16] 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.[17] 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.[3] 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.

Search strategy

To identify the case reports and case series on SGLT2i-associated euDKA, we systematically screened the PubMed/Medline and EMBASE database published up to Aug 2, 2020 for medical literature. The articles were screened by using the search string "(Euglycemic Diabetic Ketoacidosis) AND (Sglt2 Inhibitor)." Second, to identify the events of DKA we screened the PubMed and Embase for clinical trials using the string "(Diabetic ketoacidosis) AND (Sglt2 inhibitors) AND (placebo)."

Study selection

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 GDT guidelines were used for grading the main outcome as per the GRADE recommendation. Online software was used for analysis.[18] Observed data were combined with Review Manager 5 (RevMan) Version 5.3. (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).[19] 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 I^2 (the proportion of total variability explained by heterogeneity), estimated using the restricted maximum likelihood-based method. We set predecided 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 GDT (guideline development tool) software based on the principles of GRADE.[19] 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/.[20]

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.[21-67] The details are illustrated in [Figure 1]. 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].

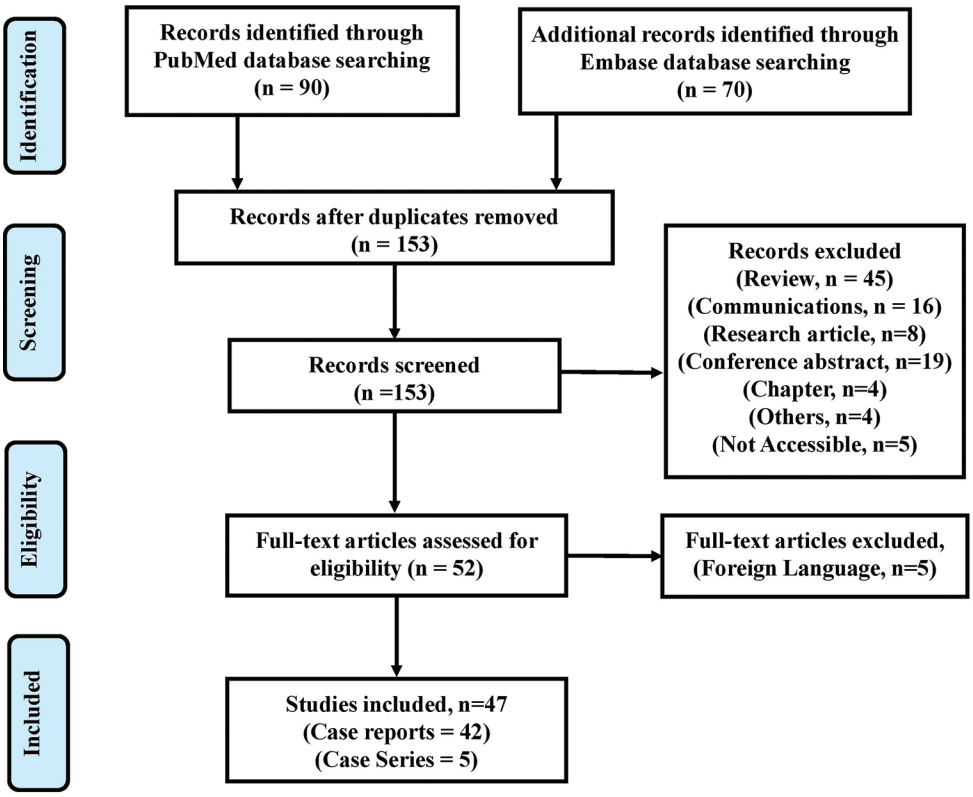

Figure 1: PRISMA flow chart depicting the study selection process

Table 1: Basic characteristics of individual case reports and case series of euglycemic DKA with SGLT-2 inhibitors

Author/Year	Age/Gender	Drug and Dose	Disease distribution	Presenting complaints
Adachi J *et al*., 2017[59]	27y, F	Canagliflozin 300 mg/day	T2DM	DKA
Alhassan S *et al*., 2018[60]	Case 1: 73y, F Case 2: 70y, M Case 3: 69y, F	Case 1: Empagliflozin 25 mg daily Case 2: Canagliflozin 300 mg daily Case 3: Canagliflozin100 mg	T2DM 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[61]	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[62]	57 y, F	Canagliflozin 150 mg BD	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[63]	27 y, F	Canagliflozin	T1DM, depression, hypothyroidism	DKA
Badwal K *et al*., 2018[64]	25 y, M	Dapagliflozin	T2DM with acute pancreatitis	One-day history of abdominal pain, nausea, and emesis
Benmoussa JA *et al*., 2016[65]	39 y, F, Caucasian	Canagliflozin	T2DM with hypothyroidism	Nausea, Vomiting, anorexia, abdominal pain and myalgia
Brown F *et al*., 2018[22]	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[23]	58 y, F	Empagliflozin 25 mg daily	T2DM with essential hypertension and obstructive sleep apnea	Altered mental status
Candelario N *et al*., 2016[21]	61 y, F	Empagliflozin	T2DM with diet-controlled hypertension	Right upper quadrant abdominal pain for a day
Chao HY *et al*., 2020[24]	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[25]	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[26]	42 y, F	Canagliflozin 100 mg	T2DM, hypertension, obesity, psoriasis, hypothyroidism, and polycystic ovary syndrome	Shortness of breath
Dai Z *et al*., 2016[27]	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[28]	44 y, F	Canagliflozin 100 mg daily	T2DM	Generalized weakness for 3 days

Contd...

Table 1: Contd...

Author/Year	Age/Gender	Drug and Dose	Disease distribution	Presenting complaints
Dizon S *et al*., 2017[29]	Case 1: 55 y, F Case 2: 38 y, F Case 3: 45 y, M Case 4: 51 y, F Case 5: 29 y, F Case 6: 54 y, M Case 7: 54 y, F Case 8: 67 y, F Case 9: 74 y, M Case 10-74 y, F	Case 1: Canagliflozin 300 mg daily Case 2: Canagliflozin 300 mg daily Case 3: Canagliflozin 300 mg daily Case 4: Canagliflozin Case 5: Dapagliflozin Case 6: Canagliflozin 300 mg daily Case 7: Dapagliflozin 10 mg daily Case 8: Dapagliflozin 5mg daily Case 9: Canagliflozin 100 mg daily Case 10: Canagliflozin 100 mg daily	T2DM, Roux-en-Y gastric bypass surgery T2DM , Roux-en-Y gastric bypass surgery T2DM T2DM T1DM T2DM, laparoscopic cholecystectomy T2DM T2DM T2DM T2DM, operative repair of an intertrochanteric fracture	Case 1: Roux-en-Y gastric bypass surgery, On POD #17, she developed nausea, vomiting, low-back pain, and dysphagia Case 2: Roux-en-Y gastric bypass surgery, 7 days after starting canagliflozin, she presented with nausea, vomiting, dizziness, and dehydration Case 3: Three-day history of shortness of breath and was found to have a mixed metabolic acidosis Case 4: Severe ketoacidosis Case 5: Nausea, vomiting and shortness of breath 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 Case 7: Presented with severe ketoacidosis Case 8: Cholecystitis, biliary sepsis, and ketoacidosis Case 9: Polydipsia, dizziness and loss of appetite 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[30]	Case 1: 55 y, F Case 2: 62 y, M	Case 1: Dapagliflozin 10 mg OD Case 2: Empagliflozin 25 mg OD	T2DM, hyperlipidemia, hypothyroidism, and anemia 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	Case 1: Nausea and vomiting Case 2: Four-day history of dysuria, urinary frequency, fever, chills, and myalgia
Earle M *et al*., 2020[31]	31y, F	Canagliflozin	T2DM	Dizziness and shortness of breath worsening over 1 week
Elshimy G *et al*., 2019[32]	28 y, F	Dapagliflozin	T2DM	Sudden-onset abdominal pain and multiple episodes of nonbloody vomitus during the previous 24 h
Fukuda M *et al*., 2020[33]	71 y, F	Canagliflozin 100 mg/day	T2DM	Malaise, nausea, and abdominal pain
Ghosh MSA, 2019[34]	52 y, M	Empagliflozin	T2DM	Weakness, poor oral intake, malaise, and tightness of chest in the evening
Iqbal I *et al*., 2019[35]	75 y, F	Dapagliflozin	T2DM, hypertension, chronic kidney disease stage III	Altered mental status and confusion
Jazi M *et al*., 2016[36]	51 y, M	Canagliflozin	T2DM and Hypertension	Malaise, cough, and intermittent shortness of breath
Karakaya Z *et al*., 2018[37]	72 y, F	Dapagliflozin	T2DM	Altered mental status two days after her hip prosthesis operation
Kelmenson DA *et al*., 2017[38]	50 y, F	Canagliflozin 300 mg daily	T2DM	Four days of nausea, vomiting, abdominal pain, and decreased oral intake
Koch RA *et al*., 2018[39]	61 y, F	Dapagliflozin	T2DM	Profound acidemia and ketonemia.

Contd...

Table 1: Contd...

Author/Year	Age/Gender	Drug and Dose	Disease distribution	Presenting complaints
Kum-Nji JS *et al*., 2017[40]	Case 1: 48 y, M Case 2: 62 y, F Case 3: 37 y, F Case 4: 52 y, F	Case 1: Canagliflozin 300 mg daily Case 2: Canagliflozin 100 mg daily Case 3: Dapagliflozin 10 mg daily Case 4: Dapagliflozin 5 mg daily	T2DM T2DM, metastatic pancreatic adenocarcinoma T2DM T2DM	Case 1: Abdominal pain Case 2: Abdominal pain revealed metastatic pancreatic adenocarcinoma Case 3: Nausea, vomiting, and weakness Case 4: Generalized weakness, malaise, polydipsia, and polyphagia
Lane S *et al*., 2018[41]	42 y, F	Canagliflozin 300 mg daily	T2DM, hypercholesterolemia, and gastroesophageal reflux	Presented for bariatric surgery with a body mass index of 40.1 kg/m2
Lau A *et al*., 2017[42]	Case 1: 54 y, M Case 2: 58 y, M Case 3: 54 y, M	Case 1: Empagliflozin 25 mg daily Case 2: Empagliflozin 25 mg daily Case 3: Empagliflozin 25 mg daily	T2DM, DKA followed by cardiopulmonary bypass (CPB) T2DM, DKA followed by coronary artery bypass grafting (CABG) T2DM, DKA followed by CABG	Case 1: Elective CABG Case 2: Elective CABG Case 3: Elective off-pump CABG (OPCAB)
Lee IH *et al*., 2020[43]	76 y, F	Dapagliflozin 10 mg/day	T2DM	General weakness, fever, oliguria, nausea, and vomiting
Levine JA *et al*., 2017[44]	60 y, M	Canagliflozin 300 mg daily	T2DM, coronary artery disease, arthritis	Total knee replacement
Lin YH, 2018[66]	37 y, F	Empagliflozin 25 mg daily	T2DM, hypertension, hyperlipidemia	Acute gastroenteritis with nausea and abdominal pain
Lucero P *et al*., 2018[45]	Case 1: 22 y, F Case 2: 50 y, F Case 3: 74 y, M	Case 1: none Case 2: Dapagliflozin 10 mg/day Case-3- none	T2DM, history of DKA, hypothyroidism T2DM, hypertension, dyslipidemia, left-side breast cancer T2DM, CKD, Cryptogenic Liver Cirrhosis	Case 1: Vomiting and abdominal pain Case 2: Abdominal pain, diarrhea, and fever Case 3: Passing liquid stools, together with emesis
Mackintosh C *et al*., 2019[46]	68 y, F	Empagliflozin 10 mg once daily	T2DM, left temporal meningioma	Left temporal meningioma
Nappi F *et al*., 2019[47]	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
Pace DJ *et al*., 2019[48]	Case 1: 66 y, F Case 2: 75 y, M	Case 1: Canagliflozin Case 2: Dapagliflozin	T2DM, pancreatic adenocarcinoma 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 Case 2-Obstructive jaundice and elevated liver function tests
Papadokostaki E *et al*., 2019[49]	64 y, M	Dapagliflozin	T2DM, HTN	Nausea, vomiting, and abdominal pain
Pereyra A M *et al*., 2017[50]	17 y, F	Dapagliflozin 10 mg/day	T1DM	Metallic taste in mouth, thick saliva, and malaise
Peters AL *et al*., 2015[51]	Case 1: 40 y, F Case 2: 58 y, M Case 3: 27 y, F Case 4: 28 y, F Case 5: 31 y, F Case 6: 55 y, F Case 7: 26 y, F Case 8: 39 y, F Case 9: 64 y, F	Case 1: Canagliflozin 300 mg/day Case 2: Canagliflozin 300 mg/day Case 3: Canagliflozin 300 mg/day Case 4: Canagliflozin 300 mg/day Case 5: Canagliflozin 300 mg/day Case 6: Canagliflozin Case 7: Canagliflozin Case 8: Canagliflozin Case 9: Canagliflozin 300 mg/day	T1DM T2DM T1DM T1DM T1DM T1DM T1DM T1DM T2DM	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 and presented to the hospital Case 8: eDKA Case 9: Elective bilateral cervical foraminotomy.
Pujara S *et al*., 2017[52]	50 y, F	Dapagliflozin 10 mg daily	T2DM	Ten days of constipation and fatigue

Contd...

Table 1: Contd...

Author/Year	Age/Gender	Drug and Dose	Disease distribution	Presenting complaints
Rafey MF *et al.*, 2019[53]	Case 1: 44 y, M Case 2: 59 y, F	Case 1: Canagliflozin 300 mg once daily Case 2: Empagliflozin 25 mg once daily	T2DM T2DM, renal oncocytoma	Case 1: Generalized weakness, lethargy, nausea, and anorexia, Six days post C5-C7 cervical decompression 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[54]	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[55]	61 y, F	Empagliflozin 25 mg per day	T2DM	Severe vomiting for 1 day
Wang KM *et al.*, 2020[67]	40 y, F	Empagliflozin	T2DM	Scheduled cerebral revascularization for moyamoya disease
Yamamoto M *et al.*, 2019[56]	51 y, M	Empagliflozin	T2DM	Nausea and vomiting
Yeo SM *et al.*, 2019[57]	23 y, F	Dapagliflozin 10 mg once a day	T2DM, acute pancreatitis due to hypertriglyceridemia	Severe abdominal pain
Zhang L *et al.*, 2018[58]	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			*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)
	Others (Multiple diseases and comorbidities)		3/77 (3.90)
Drug distribution	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%)

Number of patients/Total Number of patients=n/N; SGLT2i: SGLT2 Inhibitor

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.[6,68-82] The pooled RR was 3.70 (95% CI 2.58, 5.29). I^2 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.

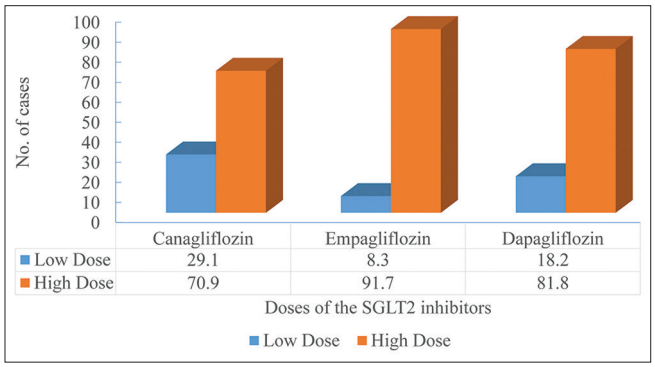

Figure 2: Dose-dependent number of euDKA cases reported in the literature

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

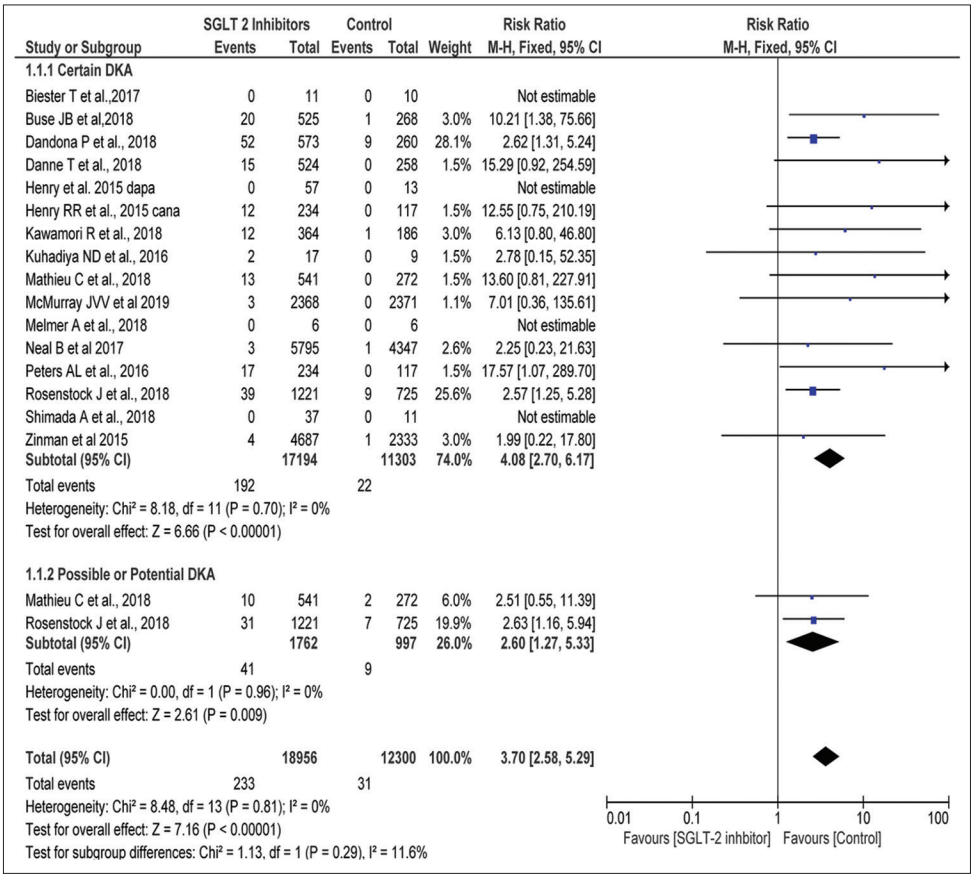

Figure 3: Incidence of DKA reported in randomized clinical trials in patients taking SGLT2 inhibitors versus control in diabetes patients

Table 3: GRADE recommendation for diabetes ketoacidosis for use of SGLT-2 inhibitors in DM patients

№ of studies Study design	Certainty assessment					№ of patients		Effect		Certainty	Importance
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Adverse events comparison in SGLT2	Placebo group	Relative (95% CI)	Absolute (95% CI)		
Events of DKA in SGLT2 inhibitors vs. Placebo											
16 RCT	not serious	not serious[a]	not serious	not serious[b]	strong association[c]	233/18956 (1.2%)	31/12300 (0.3%)	RR 3.70 (2.58-5.29)	7 more per 1,000 (from 4 more to 11 more)	⊕⊕⊕⊕ HIGH	Critical
Events of DKA in SGLT2 inhibitors vs. Placebo - Certain DKA											
16 RCT	not serious	not serious[a]	not serious	not serious[b]	strong association[c]	192/17194 (1.1%)	22/11303 (0.2%)	RR 4.08 (2.70-6.17)	6 more per 1,000 (from 3 more to 10 more)	⊕⊕⊕⊕ HIGH	Critical
Events of DKA in SGLT2 inhibitors vs. Placebo - Possible or Potential DKA											
2 RCT	not serious	not serious[a]	not serious	not serious[b]	strong association[c]	41/1762 (2.3%)	9/997 (0.9%)	RR 2.60 (1.27-5.33)	14 more per 1,000 (from 2 more to 39 more)	⊕⊕⊕⊕ HIGH	Critical

CI: Confidence interval; RR: Risk ratio; RCT: Randomized Clinical Trials Explanations: [a]As I2=0%, hence low heterogeneity. [b]As CI does not include one and overall information size is adequate; therefore, the outcome is precise. [c]As RR is greater than 2, it is regarded as large effect

Figure 4: Funnel plot depicting publication bias for studies included in the review

the patients and instruct them to report the clinician, in case they experience such symptoms. In the case of patients in postoperative care need to be screened for euDKA to avoid complications as a result of ketoacidosis. Infections were one of the precipitating factors for euDKA which was supported by the multicenteric cohort study done by Ata *et al*.[86] Treating community or primary care physicians also needs to be aware of these symptoms and high-risk individuals to avoid misdiagnosis or underdiagnosis. These symptoms and precipitating agents were similar to previously published articles.[83,87,88]

We observed that patients taking canagliflozin more prone to euDKA than dapagliflozin and empagliflozin. A multicenteric cohort study conducted by Ata *et al*.[86] also reported canagliflozin as the commonest SGLT-2 inhibitor causing euDKA. The reason for this difference may be because canagliflozin was the earliest drug approved under this class and it has been used by physicians for a longer duration than other drugs resulting in publishing more case reports.[7] We also observed the dose–response relationship with all three drugs as the incidence of euDKA proportionately increases as the dose of the drug was increased. This pattern may be because of the excessive release of glucagon in diabetic patients.[89] Wibawa *et al*. in their recent case reported euDKA with the use of empagliflozin.[90]

We also conducted a meta-analysis of randomized controlled trials, to see the overall events of DKA in patients taking SGLT2i compared to either active drug or placebo. Our findings show that patients taking SGLT2i are at the risk of experiencing DKA is about 2.58 to 5.29 times higher than the control group. This meta-analysis gives additional strength to our analysis in reinforcing the evidence showing that SGLT2i causes DKA including euDKA in both type 1 and type 2 diabetic patients. Blau *et al*.[85] showed that the risk of DKA is around 7-fold

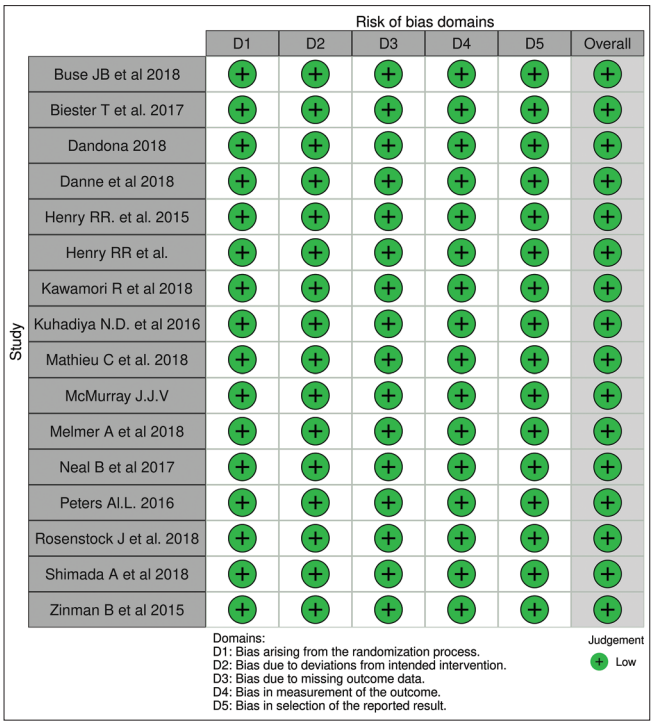

Figure 5: ROB-2: Weighted summary plot risk of bias in RCT evaluating SGLT2 inhibitors in diabetic patients

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.[91,92] 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.[93,94] Vitale *et al*.[95] 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 SGLT 2 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 execration from the plasma. A decrease in blood glucose cause decreased insulin secretion from islets which results in excess ketone body formation.[90] 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.[90] In addition, increased reabsorption of ketone bodies from the kidney due to positive electrochemical gradient generation by inhibition of SGLT 2 transporter.[96] Bonner C *et al*.[89] 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 SGLT 2 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 SGLT 2 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 multicenteric 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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Conflicts of interest

There are no conflicts of interest.

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