The Prevention of Diabetic Ketoacidosis in Patients with Type 2 Diabetes on Sodium-Glucose Transport Protein 2 Inhibitors

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Received: January 2024. Accepted: February 2024; Published: March 1, 2024.
Citation: Sara Elsheikh Ahmedana, Musa Basheer Mansour, Amr Musa Basheer. The Prevention of Diabetic Ketoacidosis in Patients with Type 2 Diabetes on Sodium-Glucose Transport Protein 2 Inhibitors. World Family Medicine. March 2024; 22(3): 62-74. DOI: 10.5742/MEWFM.2024.95257631

Abstract

Background: Sodium-Glucose Transport Protein 2 Inhibitors (SGLT2Is) effectively control diabetes. Diabetic ketoacidosis (DKA) has been reported as a life-threatening adverse effect due to SGLT2Is use.

Aim: This study aims to review the current evidence of incidence, predisposing factors and the prevention of DKA in T2DM patients on SGLT2Is use.

Methods and Materials: Two reviewers have conducted a search strategy of studies published in English between August 2012 and November 2020, in EBSCOhost, Google Scholar, PubMed, Science Direct and Wiley. Two reviewers independently assessed the eligibility and quality of the studies and extracted the data.

Results: 85 studies were identified in the initial search; 75 records were removed and finally, 10 studies were included. Only studies discussing the prevention of DKA in T2DM patients on SGLT2Is were selected, extracted and categorized into main domains that included SGLT2Is use inT2DM patients and DKA (50%), SGLT2Is use in T2DM patients (20%), the clinical presentation of DKA (20%) and DKA prevention (10%). Six studies showed SGLT2Is increased the risk of DKA with very low rates in two studies. The precipitating factors of DKA in all included studies were revealed as stopping or reducing insulin, trauma, infection, surgery, severe acute illness, vigorous exercise, dehydration, low carbohydrate intake and excessive alcohol intake. In two studies DKA can be prevented by wakefulness and education, in one study by closed follow-up, in one study by regular monitoring and adjustment of medications and in two studies by recognition of patients at risk.

Conclusions: This review summarized the prevention of DKA in T2DM patients on SGLT2Is use with consideration of incidence, a summary of evidence and predisposing factors. Physicians, health care providers and patients should be aware of SGLT2Is use, regular follow up, precipitating factors, symptoms, signs and prevention of DKA.

Keywords: Sodium-Glucose Transport Protein 2 Inhibitors SGLT2Is, Type 2 diabetes mellitus, Diabetic Ketoacidosis, Scoping Review.

Introduction

Type 2 Diabetes mellitus [T2DM] is an endocrine disorder of various causes, recognized by hyperglycemia resulting from a deficiency in insulin secretion, insulin action or both, and associated with abnormal metabolism of lipids, proteins, electrolytes, and carbohydrates [1]. T2DM is rapidly spreading globally because the estimated prevalence in 2019 was 9.3% (463 million people) and is expected to be 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045 [2]. Gliflozins or SGLT2Is are used for the treatment of T2DM [3-5] with an estimated glomerular filtration rate [eGFR] >= 20 mL/min/1 and urinary albumin 200 mg/g [6]. SGLT2Is reduce the glycated haemoglobin level (HbA1c), blood pressure, body weight and improve the renal and cardiovascular outcomes with low hypoglycaemic risk [7,8]. In 2013 they were approved by the Food Drugs and Administration (FDA) and included canagliflozin, dapagliflozin, empagliflozin and ertugliflozin [9]. SGLT2Is work at the kidneys by decreasing the reabsorption of glucose back in the blood during the filtration process. As a result, the decreased reabsorption of glucose at the kidneys means that excess glucose in the blood remains with the glomerular filtrate and is excreted as urine and causes glucose malabsorption in the gastrointestinal tract [7,10]. The adverse effects include DKA which is a life-threatening condition characterized by ketoacidosis, ketonuria, and hyperglycaemia [Ketonemia >3.0 mmol/L or significant ketonuria >2+ on standard urine sticks, blood glucose >11.0 mmol/L or known DM, Bicarbonate <15.0 mmol/L and/or venous pH <7.3. Also fracture risk, amputation risk, diuretic effect, bladder cancer, increased risk of urinary tract infections, slight elevation in lipoprotein cholesterols, electrolytes imbalance, uric acid/chronic renal disease, Fournier's gangrene, and free fatty acid elevations [9,11] can occur.

The percentage of euglycemic DKA is 0.01% and associated with blood glucose levels (<14 mmol/L), relative insulin insufficiency and precipitated by surgery or trauma, acute illnesses, alcohol abuse and dehydration [7]. DKA was a consistent nearly 2-fold increased risk (HR 2.20, 95% CI 1.25 to 3.87, p=0.006), but the event rates were low (<1 per 1000 patient years) [3].

In 2015, the FDA warned that the treatment of T2DM using SGLT2IS could increase the risk for ketoacidosis among patients [12]. In 2016 the European Medicines Agency [EMA] reported that gliflozins can cause life-threatening DKA, but the advantages exceeding the disadvantages [7]. SGLT2Is impede the reabsorption of glucose in the kidneys by decreasing the threshold for the elimination of glucose, causing glycosuria and causing a shift in the utilization of substrates from carbohydrates to the oxidation of fats, a source of energy, and the accumulation of acid in the blood and hyperglucagonemia [13].

The study showed the estimated prevalence rate and evaluated the comparative risk of DKA among individuals with T2DM in standard clinical practice. The results of the study illustrated that growth in the risk of DKA was more seen in new users of SGLT2Is than those individuals who use metformin, DPP-4 inhibitors, or GLP-1 receptor agonists [14]. With the increasing incidence of diabetes, statistics of patients with ketosis-prone diabetes also increases. There has been an increased rate of hospitalization for DKA among younger patients diagnosed with T2DM. Meanwhile, the prescription of SGLT2Is as an adjunctive medication for T2D has increased. The increase in prescription is linked with the high cases of DKA among T2DM patients [13].

This review aimed and used the available evidence to establish the relationship between DKA in patients with T2DM on SGLT2Is use. This is achieved through establishing the incidence of DKA, contributing factors, the prevention strategies of DKA for the patients and health care providers, for the appropriate use of gliflozins and best health care outcomes because DKA is life-threatening and causes long-term comorbidity and death [15,16].

Methods and Materials

This research uses scoping reviews to assess the incidence, contributing factors, and prevention strategies for DKA among patients diagnosed with T2DM using SGLT2Is. The research question included three parts; what is the incidence, the precipitating factors, and the prevention approaches of DKA in patients with long-standing T2DM on SGLT2Is?

Aims

This study reviewed the current evidence of prevention of DKA in adults' patients with T2DM on SGLT2Is use.

Objectives

The objectives were to determine the incidence, analyze the precipitating factors, and identify the prevention of DKA in patients with long-standing T2DM SGLT2Is usage.

Eligibility Criteria

The date, exposure of interest, geographical location of the study, language, participants, peer review, reported outcomes, setting, study design and type of publication were considered for eligibility. The inclusion criteria were long-standing T2DM patients over 18 years, management of T2DM with SGLT2Is and any other drugs or nonpharmacological method and DKA management. Eligible articles in this review were scholarly, peer-reviewed and were published in the English language, since 2012 to the search date. The exclusion criteria were confined to pregnant women, individuals under the age of 18 years, T1DM, and grey literature. Articles older than 10 years old were also excluded.

Study Design

This Scoping literature review considered only published studies with an aim to draw the key concepts of the studies in the broad scope of the field management of T2DM patients on gliflozins use and the occurrence of DKA. The principle of Arksey & O'Malley [17] was used and

included identifying clear research questions and aims, searching strategies, identifying appropriate research papers, studies selection, extracting and charting the data, and finally summarizing, analyzing, and presenting the outcomes on the report [17].

Literature Search Strategy

The databases EBSCOhost, Google Scholar, PubMed, Science Direct and Wiley were used, and the kinds of literature were written in English. To make the search effective, keywords [Type 2 diabetes mellitus, Diabetic ketoacidosis, Sodium-glucose transport protein 2 inhibitors], Boolean Operators, proximity, truncations were used to make the search more sensitive. Time restrictions were applied in the search, for instance the databases were restricted to provide articles published since 2012. Grey literature sources, commentary, broadcasting, editorials, conferences were excluded. The corresponding author/s might be involved and communicated with for further data details if needed.

Identification and Selection Relevant Articles/Source of Evidence Screening and Selection

Based on the eligibility criteria, aim and research question, firstly the titles and abstracts were assessed for screening and identification and secondly the full texts were assessed for eligibility. To avoid disagreement, the eligibility of the studies was discussed with two reviewers (Sara & Musa). A PRISMA flow chart was used for effective summarization of the evidence (Figure 1). Primary studies presented an opportunity to quantify the effect of the SLGT2Is on the patient and the risk of causing DKA while most recent studies provided the best opportunity for a reliable review.

Data Extraction (Charting) and Collection Process

The included studies were compiled and extracted in (Table 2). The extracted data were linked to the research questions and aims, and included citations, titles, country of study, the aims, population characteristics, designs, settings, sample size, sample techniques, data sources, measures, analysis, confounder variables, and key observations. The narrative review or descriptive-analytical method was used to extract contextual or process-oriented information from each study (Table 2).

Summarizing, Analyzing and Presenting the Findings

The included studies were categorized into five main domains i.e. SGLT2Is use for patients with T2DM and rate or risk of DKA, precipitating factors and prevention of DKA, and assessment of SGLT2Is.

The methodological studies characteristics were also evaluated in a table and each study was assessed for the design, sample size, the target of the study and the setting. Then the data were classified and presented in percentage

Results

Literature Search Results

The authors demonstrate in (Figure 1) a total of eighty-five studies were identified and involved in the initial search for this scoping review revealing thirty from PubMed, twenty from Science Direct, ten from EBSCOhost, five from Wiley and twenty from Google scholar. A total of thirty-five duplicated records was removed with a remaining fifty records. The remaining records after screening were twenty-six and the excluded records after the screening process was twenty-four. Full-text articles assessed for eligibility were twenty-six and sixteen full-texts were excluded in the eligibility process. Finally, ten studies were included in the synthesis.

Characteristics of Included Articles

The included studies were categorized (Table 1); (n 5, 50%) of the articles discussed Gliflozins use in T2DM and DKA, (n 2, 20%) discussed the gliflozins use in T2DM, (n 2, 20%) discussed the clinical presentation of DKA and (n 1, 10%) discussed DKA prevention. The countries of origin were (n 4, 40%) not available (N/A), (n 2, 20%) in United States, (n 1, 10%) in China, (n 1, 10%) in India, (n 1, 10%) in Syria and (n 1, 10%) in Greece. The population characteristics were the prevention of DKA in T2DM patients on SGLT2Is use. The design was (n 3, 30%) case report, (n 2, 20%) systematic review, (n 2, 20%) systematic review and metanalysis, (n 1, 10%) retrospective study, (n 1, 10%), prospective study and (n 1, 10%) literature review. The setting of the studies was (n 3, 30%) hospital and (n 7, 70%) N/A. Sample size was thirty-four individual case reports, seven trials, one patient, 60,580 patients, one patient, one N/A, sixty patients, 34,322 patients, 115 admissions and one patient.

Data Extraction of the Included Articles

The data were extracted in tables under the following sub-titles citation number, citation, titles, country of origin, aims of the study, population characteristics, design, setting, sample size, sample technique, measures, analysis, confounders, and key observation (Table 2).

Table 1: Methodological Characteristic of The Included Articles(n=10)

Characteristics	Categories	n	%
Country of Origin	N/A	4	40
	USA	2	20
	China	1	10
	India	1	10
	Syria	1	10
	Greece	1	10
Study Design	Case report	3	30
	systematic review	2	20
	systematic review and meta-analysis	2	20
	retrospective study	1	10
	prospective study	1	10
	literature review	1	10
Sample size	60,580 patients	1	10
	34,322 patients	1	10
	60 patients	1	10
	One patient	3	30
	115 admissions	1	10
	34 individuals	1	10
	7 trials	1	10
	One N/A	1	10
Setting/Target	Hospital	3	30
	N/A	7	70
Study discussed specific title	Gliflozins use in T2DM and DKA relationship	5	50
	Gliflozins use in T2DM.	2	20
	Clinical presentation of DKA	2	20
	Prevention of DKA	1	10

Figure 1: PRISMA Flow Chart of Scoping Review

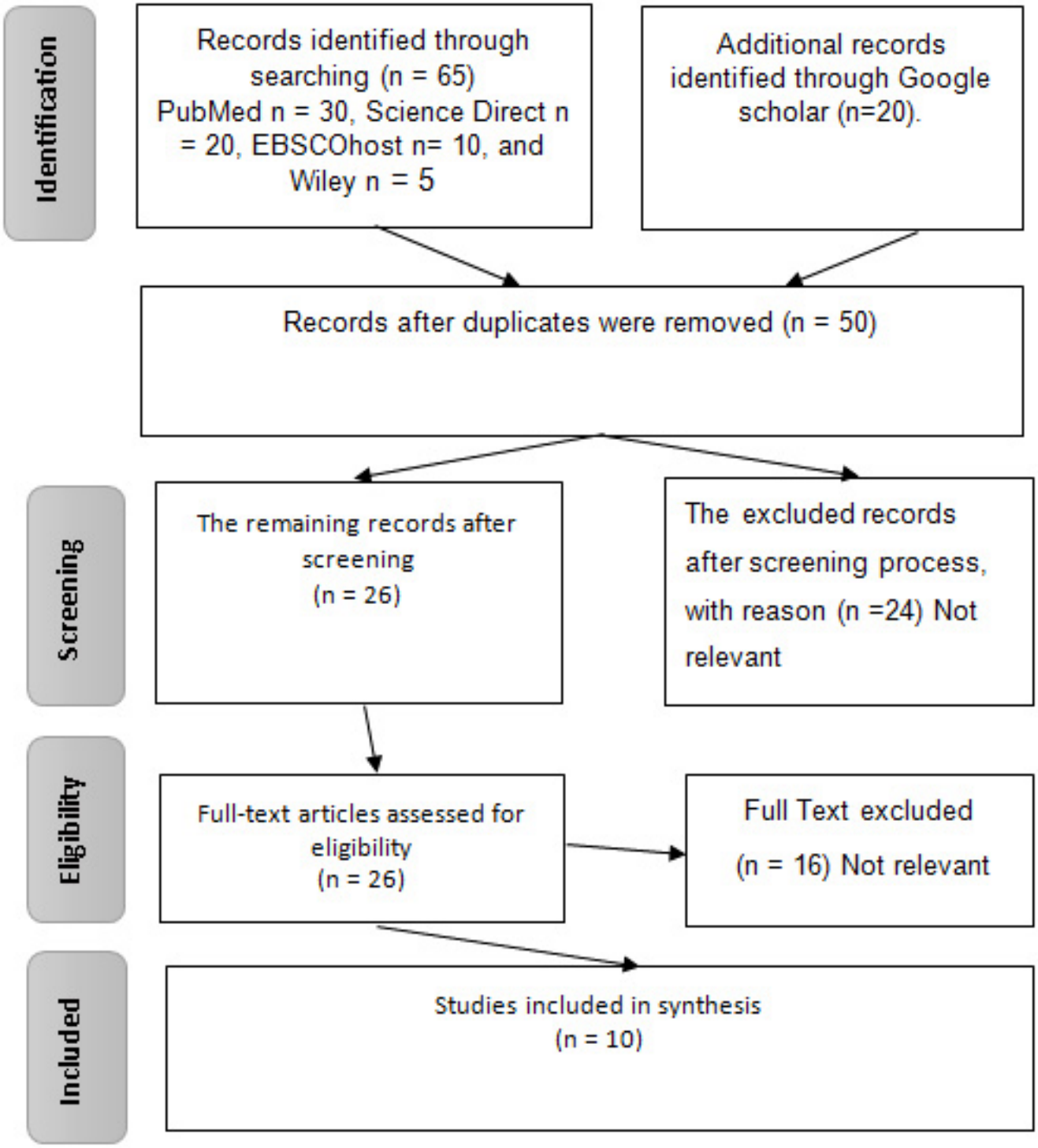

Table 2: Data Extraction of included articles

Citation	Title	Country of origin	Aim of Study	Population characteristics	Design	Setting	Sample Size	Sample technique	Data source	Measures	Analysis	Confounder Variables	Key observation
Burke et al. 2017	SGLT2 Inhibitors: A Systematic Review of Diabetic Ketoacidosis and Related Risk Factors in the Primary Literature.	United States	Better understand the clinical presentation and characteristics of DKA caused by SGLT2 inhibitors.	Type 2 diabetes patients treated with SGLT2i and developed DKA	Systematic review of primary literature	NA	34 individual case reports	Search on numerous databases using the key words canagliflozin, dapagliflozin, empagliflozin, SGLT2, sodium glucose cotransporter2 inhibitor, diabetic ketoacidosis, ketoacidosis, metabolic acidosis, and acidosis.	Primary literature	Blood glucose levels on the presentation for SGLT2i-induced DKA	Descriptive analysis	NA	Canagliflozin was implicated in cases of DKA. There was no precise link between the occurrence of DKA and the interruption of SGLT2i that could be identified.
Clar et al. 2012	A systematic review of SGLT2 receptor inhibitors in dual or triple therapy in type 2 diabetes.	N/A	Assessing the clinical safety and effectiveness of the SGLT2 receptor inhibitors in dual or triple therapy in type 2 diabetes.	Adults of any ethnic origin above the age of 18 diagnosed with type 2 diabetes	Systematic review	NA	7 trials	Randomized control trials of SGLT2i compared to a placebo or active comparator among T2D patients in combination with dual therapy	MEDLINE, Embase, Cochrane Library	Quality assessment was done using the Cochrane risk of bias score	Metanalysis was done	Costs of SGLT1i are not known Lack of long-term data on the safety of SGLT2i	7 trials fully assessed and published dapagliflozin. Canagliflozin was assessed by one. Both canagliflozin and dapagliflozin resulted in the loss of weight but dapagliflozin appears to be more effective.

Elasha et al. 2018	SGLT2 inhibition may precipitate euglycemic DKA after bariatric surgery.	N/A	To describe potential risk factors for DKA by identifying individual patient characteristics associated with cases of SGLT2i-related DKA.	An obese male patient with poor management of T2D using SGLT2i dapagliflozin	Case report	Hospital	I patient	NA	Patient hospital records	Effectiveness of SGLT2 inhibition treatment plan	Case Study Analysis	The limited scope of the study	Precipitating factors included patients with T2DM, those who recently had major surgery, had latent autoimmune diabetes of adulthood and, had decreased or discontinued insulin
Liu et al. 2020	SGLT2 inhibitors and risk of diabetic ketoacidosis in patients with type 2 diabetes: systematic review and meta-analysis of randomized controlled trials.	China	Assessing the effects of SGLT2 inhibitors on DKA in patients with T2D.	T2D patients	A systematic review and meta-analysis	NA	60580 patients	Randomized Controlled Trials	Cochrane Central Register of Controlled Trials, EMBASE and PubMed	Peto's method Mantel-Haenszel method	Grade analysis	The difference in age has different treatment outcomes	SGLT2 inhibitors increase the risk of DKA in patients with T2D.

Gajjar et al. 2019	Euglycemic Diabetic Ketoacidosis in the Setting of SGLT2 Inhibitor Use and Hypertriglyceridemia: A Case Report and Review of Literature	N/A	To discuss the diagnosis, pathophysiology, prevention, and management of DKA induced by the use of SGLT2 inhibitors.	A 28-year-old female with T2D	A case report and literature review of euDKA among patients using SGLT2 inhibitors.	NA	1 patient	NA	Patients medical history and literature review	Predisposition to the euDKA risk factors	Case report and descriptive analysis	The patient diagnosis did not check c-peptide, glutamic acid decarboxylase antibodies, and islet cell antibodies which are relevant for diabetes mellitus. diagnosis	Risk factors for euDKA include the reduction or omission of insulin, dehydration, severe acute illness, surgery, extreme physical activity, low carbohydrate diets, or excessive alcohol intake. EuDKA caused by SGLT2 inhibitors is rare. This is largely reported in the setting of known precipitants.
Gosmanov et al. 2014	Management of adult diabetic ketoacidosis	N/A	Providing an overview on DKA from its pathophysiology to clinical presentation with a depth focus on up-to-date therapeutic management.	N/A	Literature review on DKA.	NA	NA	NA	NA	Effective management of Diabetic ketoacidosis (DKA) measures including up-to-date therapeutic interventions	Descriptive analysis	The study assumed that timely adjustment of insulin dose, fluids, electrolytes frequent monitoring of blood glucose levels, patient and provider education can effectively prevent DKA.	DKA management based on its pathophysiology is complex and requires carefully selected approaches that aim to restore deficiencies in insulin, fluids, and electrolytes. Therefore, individualized management is recommended due to the varying and unique patient characteristics.

Seth et al. 2015	Clinical Profile of Diabetic Ketoacidosis: A Prospective Study in a Tertiary Care Hospital.	India	Looking into the precipitating factors, and clinical profile and outcome in DKA patients in the emergency room of tertiary care hospital.	Diabetes patients diagnosed with DKA	A prospective study	Hospital	60 patients	NA	Patients medical history and current diagnosis	Diagnostic criteria for DKA Blood glucose more than 250, arterial ph less than 7.3, serum bicarbonate less than 15 mEq/l	Calculation of percentages	Did not involve patients using SGLT2i	Early diagnosis and treatment can reduce mortality and morbidity.
Zelniker et al. 2019	SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials.	United States	To assess the magnitude of the effect of SGLT2i on particular renal and cardiovascular outcomes and whether key baseline characteristics determine heterogeneity.	T2D patients	A meta-analysis and systematic review	NA	34322 patients	randomized, placebo-controlled, cardiovascular outcome trials of SGLT2i in patients with T2D.	3 Trials	NA	NA	Poor data analysis	SGLT2i have moderate benefits on atherosclerotic major adverse cardiovascular events. They are vital in reducing the progression of renal disease and hospitalization for heart failure irrespective of a history of heart failure or existing atherosclerotic cardiovascular disease.

Alouni, 2015	Precipitating factors, outcomes, and recurrence of diabetic ketoacidosis at a university hospital in Damascus.	Syria	Studying the precipitation factors, outcome, and recurrence of diabetic ketoacidosis (DKA).	T2D patients with DKA	This was a retrospective study	Hospital	115 admissions	100 DKA patients that fulfilled the American Diabetic Association DKA diagnostic criteria	Medical records	NA	Statistical package for social science Chi-square	The limited scope of the study	Infections followed by insulin-related problems were the predominant precipitating factors for DKA patients in all admissions, which was similar to other studies. But the mortality rate was higher due to the severity of underlying precipitating illness.
Papadokostaki et al. 2019	Euglycemic Diabetic Ketoacidosis Secondary to Dapagliflozin in a Patient with Colon Malignancy.	Greece	To assess the negative effects, in this case, euglycemic diabetic ketoacidosis , of using SGLT2 even though its use has increased.	64-year-old-man with a 3-day history of abdominal pain, nausea, and vomiting.	A case report	NA	1 patient	NA	Patients medical records and history	NA	NA	The limited scope of the study	Euglycemic diabetic ketoacidosis is a likely effect of using SGLT2 inhibitors. Clinicians must identify patients with the risk of euglycemic DKA and provide the relevant advice.

The Domains of the Review

SGLT2Is use for patients with T2DM and risk of DKA
Ten studies were included in this review; six out of them show that the use of SGLT2Is in T2DM patients increases the risk of DKA [3,4, 15, 18-20,22]

SGLT2Is use for patients with T2DM and rates of DKA
Two out of the ten studies show that the rates of DKA are very low [3,4].

SGLT2Is use for patients with T2DM and precipitating factors of DKA
The precipitating factors are many, and all the included studies revealed that stopping insulin, or reducing insulin dose, trauma, infection, surgery, severe acute illness, vigorous exercise, low fluids intake and dehydration, low carbohydrate intake, excessive alcohol intake play a major role in the occurrence of DKA [3,4,15,18-23].

SGLT2Is use for patients with T2DM and prevention of DKA
In two included studies, it was shown that DKA can be reduced and prevented by wakefulness and education [3.22], by a closed follow-up in one study [4], by regular monitoring and pre-emptively adjustment of medications in one study [14] and by recognition of patients at risk in two studies [18,19].

Assessment of SGLT2Is (Table 3):
The development and application of the eligibility criteria were appropriately used throughout the selection of the studies. The assessment of SGLT2Is causing DKA among T2DM patients was adequately determined in two studies [18,19], the adverse effects were mentioned in four studies [3,20-22] and the risk factors for DKA among T2DM patients using SGLT2Is were highlighted in two studies [4,15] and one study determined the prevention strategies [23].

Discussion

The included studies of this review used various designs to manage and prevent DKA in patients with T2DM on SGLT2Is.

Incidences and Risk of DKA and summary of evidence
DKA is an issue of concern among T2DM patients using SGLT2Is. This is because DKA is a rare occasion among patients with T2DM. Although there is no precise link between using SGLT2Is and DKA development, it is evident from the results that SGLT2Is increase the risk for DKA [15]. SGLT2Is are designed for individuals with T2DM [23]. SGLT2Is prevent the reabsorption of glucose from the primary urine at the proximal renal tubes, reduce body weight and are accompanied by pleiotropic effects that are attributable to weight loss. These pleiotropic effects might include non-alcoholic fatty liver disease, amelioration of insulin resistance, and dyslipidemia. In relevance to recent evidence, it has been suggested that individuals on SGLT2Is are at more risk of developing the condition. In EMPA-REG OUTCOME trial [Empagliflozin] Cardiovascular Outcome Event Trial in T2DM Patients [7,020 patients], five events of DKA were occurred and the treatment events per 1000 patients/year was 0.10. In CANVAS Program Canagliflozin and Cardiovascular and Renal Events in T2DM [10,142 patients], 18 events of DKA were occurred and the treatment events per 1000 patients/year was 0. 60. In DECLARE-TIM 58 (Dapagliflozin Effect on Cardiovascular Events) [17,143 patients], 48 events of DKA were occurred and the treatment events per 1000 patients/year was 0.90 [3]. Very few SGLT2Is users have a risk of developing DKA which is associated with an increased level of glucagon [15]. DKA influenced by the amalgamation of ketosis and metabolic acidosis in euglycemic patients with low intake of food, dehydration, decreased insulin doses, vomiting, loss of weight, infection, surgical procedure or operation, or poorly controlled diabetes [15,23,24]

The incidence of DKA in T2DM patients on SGLT2Is is 0.1% in 1000 patients/year [21]. For DKA there was a consistent nearly 2-fold increased risk (HR 2.20, 95% CI 1.25 to 3.87, p=0.006), but the event rates were low (<1 per 1000 patient years) [3]. From March 2013 to May 2015 FDA reported forty-four cases of euglycemic DKA. In 2015 May EMA reported 101 cases of life-threatening conditions worldwide in EudraVigilance with an estimated exposure above 0.5 million patient-years [25]. Eighty-five DKA events were registered as an outcome of thirty-nine RCTs that involved 60580 participants [18].

Predisposing factors of DKA in T2DM patients use SGLT2Is
The exact mechanism in which SGLT2Is increase the risk of DKA among T2DM patients is yet to be established. Several factors might increase the risk of developing DKA among patients diagnosed with T2DM taking SGLT2Is. The risk factors include a history of alcohol abuse which generally promotes hypoglycemia, and increased demand for insulin due to an acute illness, restricted intake of carbohydrates, stress, dehydration, surgery, or a sudden decrease or loss in insulin levels in the body [15,22].

Prevention of DKA among T2DM patients using SGLT2Is.
Early detection and management of DKA can avoid complications and mortality [23].

Since DKA has fatal consequences, the primary prevention strategy is effective communication, proper patient education on the symptoms, effects, and consequences of DKA. During patient education, it is important to enlighten the patients on the early signs and symptoms which include polyuria, polydipsia, nausea, vomiting, weakness, dehydration, hypotension, abdominal pain, feeling or being sick, fast, and deep breathing [15,23]. Stopping SGLT2Is before surgery and repetition postponement until patients are fit to preserve evenness of diet, adequate carbohydrate intake and fluids without prolonged catabolic

Table 3: Assessment of SGLT2Is in the included articles

Citation	The assessment of SGLT2Is causing DKA among T2DM patients,	Addressing Side Effects associated with SGLT2Is.	The risk factors for DKA among T2DM patients using SGLT2Is.	Failure to adequately address the topic	Prevention strategies for DKA	Incomplete Follow up
Burke et al., 2017	+	+	+	+	_	-
Clar et al. 2012	+	+	-	-	?	?
Elasha et al. 2018	+	+	-	?	+	?
Liu et al. 2020	+	+	_	+	_	?
Gajjar et al. 2020	+	+	+	+	_	_
Gosmanov et al. 2014	+	+	_	_	+	?
Seth et al. 2015	+	+	_	+	?	?
Zelniker et al. 2019	+	+	_	_	_	?
Alourfi, 2015	-	+	+	?	_	_
Papadokostaki et al. 2019	?	+	+	+	+	?

Low risk (+), high risk (-) and unclear (?).

state [20]. Additionally, follow the sick day role includes frequent testing of blood sugar and urine for ketones, increased state [20]. Additionally, follow the sick day role includes frequent testing of blood sugar and urine for ketones, increased carbohydrate and fluids and never stop insulin but considerably increase the dose, during illness even without eating. Also, patients and family's education about symptoms and signs reduces DKA [15, 26].

Limitations

This review includes papers published in the English language that may exclude some studies. Also, this review provided a broad scope of T2DM patients on SGLT2Is use, predisposing factors, the incidence, and prevention of DKA. Furthermore, the number of included papers is occasionally small because some published papers require purchase, and the fund was not available. The quality assessment and critical appraisal of the 10 studies consists of sex elements for each study; high risk was 18, unclear was 12 and low risk was 30. Moreover, the included studies did not include or mention biases that can affect internal or generalized validity. In four studies the country of origin was not determined, seven studies were without a setting, one did not specify the sample size, five did not specify sample technique and two studies were without analysis. Additionally, grey literature was not included due to many reasons that included the time factor to find articles, the multiple search engines, hand searching and the need for communications with the corresponding authors. Finally, due to the lack of sufficient literature and the inclusion of few studies in this review, this limits the scope and the extensiveness in highlighting the consequences of using SGLT2Is among T2DM patients.

Conclusion

This scoping review summarized the use of SGLT2Is among T2DM patients, the incidence, the summary of the evidence, the predisposing factors, and the prevention of DKA. DKA among SGLT2Is users, is rare and life-threatening, has unclear mechanisms/ pathophysiology and can be intractable to diagnose. Clinicians should be aware of T2DM on SGLT2Is users with hemodynamic stability, normal vital signs, asymptomatic and comparatively normal blood glucose levels and should check the ketones levels in suspected patients. SGLT2Is users should be observed closely and advised regarding symptoms such as nausea, vomiting, abdominal pain, tachypnea, and lethargy. In addition to DKA triggers factors such as alcohol abuse, infections, trauma, and reduced fluids intake. Physicians, clinicians, health care providers, pharmacists, pharmacological companies, and policymakers could consider the results of this review to manage and guide the people with T2DM who use SGLT2Is. Patients should look out for and recognize DKA symptoms, avoid the factors that precipitate DKA and follow the physician's advice and guidance. Safety could be an essential area of future research.

Implications of the findings for research

The future conduct of primary research, or systematic review may be appropriate based on gaps in knowledge identified from the results of the review.

Acknowledgements
I appreciate the Teaching Staff of Master of Science in Diabetes Care at The University of Warwick in UK for The Continuous Support and Great Co-Operation and Assistance.

Funding
There was no funding source for this research.

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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