Received: 22 November 2024 | Revised: 7 February 2025 | Accepted: 9 February 2025

DOI: 10.1111/dom.16282

ORIGINAL ARTICLE

WILEY

A systematic literature review on the burden of diabetic ketoacidosis in type 2 diabetes mellitus

Carol Wysham MD[1] | Anila Bindal MD[2] | Fleur Levrat-Guillen PharmD[3] | Desislava Kostadinova MBiol[4] | Yeesha Poon PhD[2]

[1]Section of Endocrinology and Metabolism, MultiCare Rockwood Clinic, Spokane, Washington, USA

[2]Abbott Diabetes Care, Alameda, California, USA

[3]Abbott Diabetes Care, Maidenhead, UK

[4]PharmaGenesis Oxford Central, Oxford, UK

Correspondence
Yeesha Poon, Abbott Diabetes Care, 1420 Harbor Bay Parkway, Alameda, CA, USA.
Email: yeesha.poon@abbott.com

Funding information
Abbott Diabetes Care

Abstract

Aim: To understand the existing literature on the epidemiology and clinical, humanistic, and economic burden of diabetic ketoacidosis (DKA) in people living with type 2 diabetes mellitus (T2DM).

Materials and Methods: MEDLINE, Embase and the Cochrane library were systematically searched for studies published between 1 January 2014 and 14 December 2023. Clinical trials and observational studies, conducted in people living with T2DM, were included if they provided data on DKA epidemiology, morbidity, mortality, hospitalizations or patient-reported outcomes. Studies of DKA-associated costs in T2DM were also included. Data were summarized descriptively.

Results: Overall, 197 publications were included. We found wide variations in DKA prevalence (0.0%–50.0%; 5th–95th percentile: 0.02%–26%; 126 publications) and incidence (0.0–24.5 events per 1000 patient years; 5th–95th percentile: 0.004–7.6 events per 1000 patient years; 37 publications). Populations at increased risk of DKA included patients using sodium–glucose cotransporter-2 inhibitors, those using insulin and those with poor glycaemic control. The most common precipitating factors were infection and non-adherence to treatment. There was limited evidence on the humanistic burden of DKA, but the results highlighted a high burden of complications including acute kidney injury or failure. The length of hospital stay ranged from days to several weeks.

Conclusions: DKA is associated with a high clinical burden in people living with T2DM. Resources to screen for and potentially prevent DKA may reduce the burden of DKA for patients with T2DM and the healthcare system.

KEYWORDS

diabetic ketoacidosis, disease burden, DKA, epidemiology, risk factors, type 2 diabetes mellitus

1 | INTRODUCTION

Currently, an estimated 537 million adults worldwide are living with diabetes, more than 95% of whom have type 2 diabetes mellitus (T2DM).[1,2] People living with diabetes are at risk of developing diabetic ketoacidosis (DKA), a life-threatening complication that is characterized by hyperglycaemia (in most cases), hyperketonaemia and acidosis, and requires timely care.[3,4] DKA risk varies according to

diabetes treatment, comorbidities and age.[5] Subgroups at risk of DKA would benefit from ketone monitoring, but few people with diabetes regularly monitor their ketone levels because of a lack of awareness of the importance of ketone monitoring and how to interpret and take action on ketone levels.[6] The current methods for ketone monitoring can be costly and burdensome and are often not reimbursed.[6] In addition, these methods do not indicate the onset of ketosis or ketoacidosis, but rather confirm if it is already in progress.[7]

Although people living with type 1 diabetes mellitus (T1DM) and T2DM are both susceptible to DKA,[3] the burden of DKA in T2DM is not well defined. To understand the health impact of DKA on patients and the healthcare system, a systematic literature review (SLR) was designed to identify and summarize existing evidence on the prevalence, incidence and burden of DKA in T2DM and to identify those with T2DM at risk of DKA.

2 | METHODS

2.1 | Objectives

The objective of this SLR is to understand the existing literature on the burden of DKA in people living with T2DM, including epidemiology (incidence, prevalence and risk factors) and clinical, humanistic, and economic burden. Specifically, patients receiving sodium–glucose cotransporter-2 inhibitors (SGLT2is) and those using insulin were investigated, because DKA is known to be associated with SGLT2i use and missed or inadequate doses of insulin in patients with T2DM, as noted in the American Diabetes Association (ADA) "Standards of Care in Diabetes".[8] Several additional factors (age, race/ethnicity, body weight, prior DKA, glycaemic control, ketosis, ketosis-prone T2DM, pregnancy status, renal status, alcohol consumption, starvation, high blood lactate, newly diagnosed T2DM or duration of T2DM) were specified post hoc (after data extraction).

2.2 | Searches and screening

MEDLINE, Embase and the Cochrane Library were searched via Ovid for the period of 1 January 2014 to 14 December 2023. The searches were designed to identify clinical trials and observational studies, conducted in people living with T2DM, that provided data on DKA epidemiology, monitoring, morbidity and mortality, hospitalizations with DKA and patient-reported outcomes/quality of life in those with DKA. The searches were also designed to identify studies of the costs associated with DKA in T2DM. Case reports and non-English language publications were excluded. Search strings are presented in Tables S1–S3.

We also identified the following as congresses of interest: ADA 2021–2023; Advanced Technologies & Treatments for Diabetes 2021–2023; and European Association for the Study of Diabetes (EASD) 2021–2023. The proceedings of all congresses of interest were indexed in Embase and captured in the electronic searches.

The abstracts of the identified publications were screened to determine whether they met predefined eligibility criteria (Table S4). If they did, the full-text versions of those papers were then reviewed against the same criteria to confirm their eligibility. Both screening stages were performed in a single-blind manner by one reviewer; 8% of the title/abstract screening decisions were checked by a second, senior reviewer. Discrepancies were noted in only 1% of the title/abstract screening sample. Any uncertainties on screening decisions were resolved by the senior reviewer.

2.3 | Data extraction

Data regarding study design, patient characteristics and measures of the clinical, economic, humanistic and epidemiologic burden of DKA were extracted from the included studies. Epidemiologic data included DKA incidence, prevalence, risk factors (factors associated with an increased likelihood of developing DKA) and precipitating factors (events or conditions [e.g., infection] that trigger a DKA episode).

Data were extracted into a Microsoft Excel document by one reviewer and quality-checked by a second reviewer. Outcomes were reported descriptively as ranges with 5th and 95th percentiles (obtained by numerically sorting estimates from individual studies and discarding the top and bottom 5% without weighting) to limit the impact of outliers. No meta-analysis was performed.

3 | RESULTS

Initial searching identified 1397 hits. After removal of duplicates, 1245 studies underwent title/abstract screening, 392 studies underwent full-text review and 197 publications were identified as eligible for data extraction (Figure 1). Most of the studies were published from 2021 up to the cut-off date of 14 December 2023 (Figure 2). Studies were distributed approximately equally among global regions with the exception of Latin America (Figure 2). Similarly, there was variation in study designs. Most studies were retrospective (78%); other designs included prospective studies, randomized controlled trials and single-arm studies (Figure 2).

The definition of DKA was generally consistent across publications (91 publications)[9–99]: blood glucose >250 mg/dL, pH <7.3, anion gap >10 mmol/L, bicarbonate level ≤18 mmol/L and ketonemia/ketonuria. The most frequently used International Classification of Diseases (ICD) diagnostic codes were ICD, Ninth Revision 250.1 (6 publications)[26,27,29,31,33,92] and ICD, Tenth Revision E11.1 (6 publications).[29,44,47,84,100,101]

3.1 | Prevalence and incidence

The prevalence and incidence of DKA in patients with T2DM varied widely. For prevalence (126 publications),[10–12,17–139] the range was

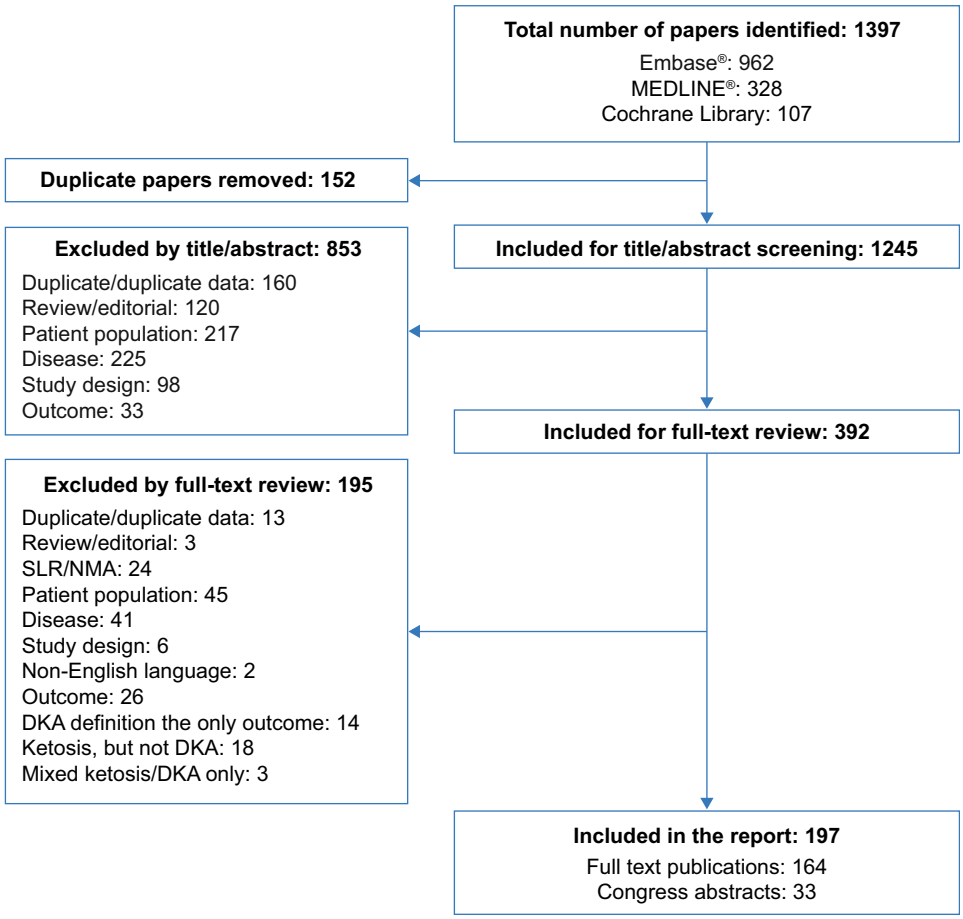

FIGURE 1 PRISMA flow diagram. †Population with T1DM only or mixed T1DM and T2DM with no subgroup data. ‡Not diabetes or not DKA, ketosis, ketoacidosis or acidosis. §Case studies/reports. ¶A definition of DKA was reported, but there were no other outcomes of interest in the publication (i.e., no epidemiology, clinical, humanistic or economic burden outcomes). DKA, diabetic ketoacidosis; NMA, network meta-analysis; PRISMA, Preferred Reporting Items for Systematic Review and Meta-analyses; SLR, systematic literature review.

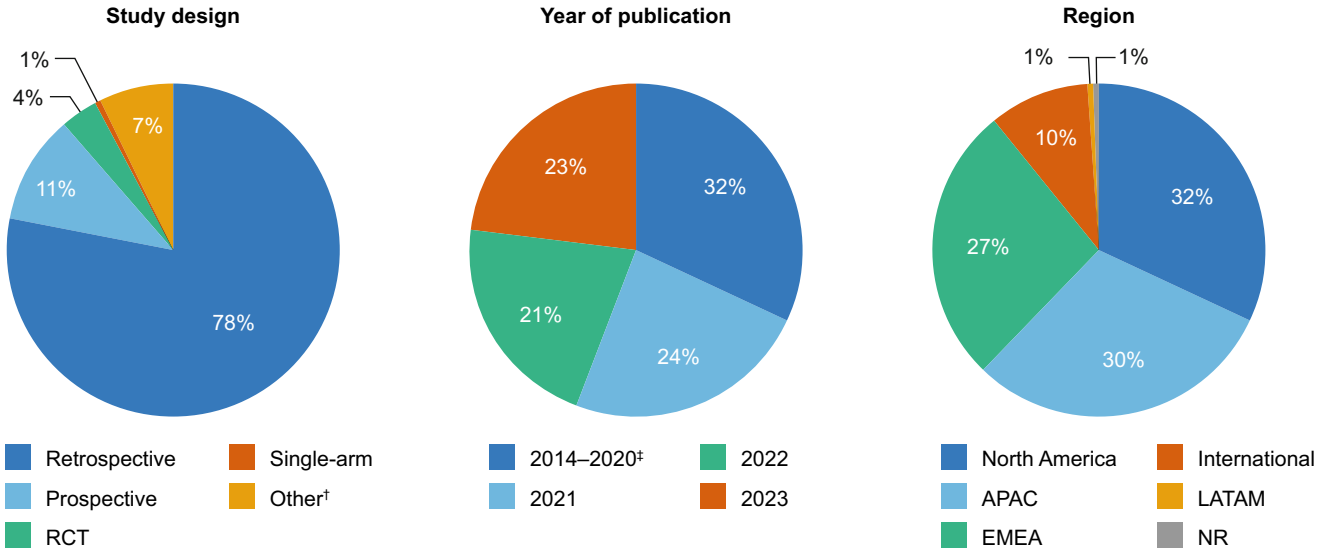

FIGURE 2 Overview of included publications by year of publication, region and study design. †Others include pooled RCTs (3.6%), publications with both retrospective and prospective elements (2.0%), and unclear observational designs (1.5%). ‡Published in 2014 (3%), 2015 (2%), 2016 (4%), 2017 (7%), 2018 (3%), 2019 (8%) and 2020 (5%). §The cut-off date for the literature searches was 14 December 2023. APAC, Asia–Pacific; EMEA, Europe, the Middle East and Africa; LATAM, Latin America; NR, not reported; RCT, randomized controlled trial.

0.0%–50.0% (5th–95th percentile: 0.02%–26%).[10,13,14,17,19–24,29–36,40,41,45,46,51–53,56,57,59,62,64–68,70,76,78,79,82,84,87,89–91,94–99,101–176] For incidence (37 publications),[10,11,17,18,38,42,46,47,53,56,71,74,75,80,83,84,102–106,111,122,124,125,130,134,138,140–148] the range was 0.0–24.5 events per 1000 patient years (PY) (5th–95th percentile: 0.004–7.6 events per 1000 PY),[9,29–31,35,43,52,56,59,60,84,89–91,101,114,115,120,123,134,

TABLE 1 Summary of DKA prevalence and incidence by country/region.

Country/region	Prevalence or incidence, range	Citation
Prevalence (%)		
Australia	0.3–15.4	30,46,64
China	0.0–50.0	34,36,41,57,94,95,97–99,106,112,113,128,129,169,176
Croatia	4.8	139
Denmark	0.1–0.5	56,159
Ethiopia	1.8–28.4	53,107,124
France	0.2–1.7	101,126,127,162
Germany	0.1–0.3	89
Ghana	2–43.8	13,105
Hong Kong	0.04–20.7	59,115,141
Hungary	0.7	135
India	1–13.3	68,70,187
Indonesia	14.6	158
Italy	1	33
Japan	0.2–31.4	45,84
Malaysia	13.4	173
Philippines	3.9	164
Qatar	0.3–21.4	17
Saudi Arabia	0.2–22.1	22,103,104
Singapore	0.6–0.7	125
South Korea	0.04–7	132–134
Spain	0.01–5.6	116,149
Sri Lanka	0.13	111
Taiwan	10.8	96
Thailand	9.7–13.7	160,167
The Gambia	2.6	10
Turkey	2.4	152
UK	0.2–3.0	40,51,144,175
USA	0.0–47.1	14,19,21,23,24,29,31,32,62,65–67,78,79,82,90,91,102,108–110,117,118,123,130,136,138,140,143,145–147,150,151,153–157,163,165,166,168,172
Incidence (events per 1000 PY)		
Australia	0.83	30
Denmark	0.53–3.47	56
Ethiopia	63	9
France	11.2–19.8	101
Germany	0.5–2.8	89
Hong Kong	0.2–24.5	59,60,115
Japan	0.38–0.48	84,182
South Korea	0.6–2.7	43,134
Switzerland	0.001–0.07	179
UK	0.85	175
USA	0.55–9.1	18,19,29,47–49,77,143,149,150,152,158,159

Note: Ranges include data from patient subgroups if the prevalence/incidence for the overall population was not reported. Treatment subgroups are included. For DKA prevalence, the UK category includes one publication that includes data from Scotland only. Incidence estimates reported in units other than events per 100 PY, per 1000 PY, per 10 000 PY or per 100 000 PY are excluded.

Abbreviations: DKA, diabetic ketoacidosis; PY, patient years.

137,142,153–157,161,171,174,175,177–182 with an outlier of 63 events per 1000 PY in Ethiopia.[9] The authors of the Ethiopian study—which was a retrospective analysis of data from 2016 to 2020—commented that the high incidence could be due to their hospital-based study design and disparities in economic status, level of education and access to healthcare facilities compared with other study populations.[9]

The prevalence and incidence of DKA were reported for 28 and 11 countries/regions, respectively. Both varied between countries and across publications within the same country (Table 1). The highest prevalence of DKA was reported in China (50.0%); however, the publication exclusively included patients with ketosis-prone T2DM (diabetes without precipitating illness and with ketosis or DKA in the absence of autoantibodies at diagnosis)—these patients had a high likelihood of DKA by definition.[97] The next highest prevalence values were reported in the USA, in patients newly diagnosed with T2DM during the COVID-19 pandemic (2020; 47.1%)[130] and in patients aged <21 years with T2DM who were hospitalized with COVID-19 (46%)[102]; delays in accessing medical care during the COVID-19 pandemic and (in the latter study) the hospital-based setting and presence of infection may have contributed to the high prevalence of DKA. The lowest prevalence of DKA (0.0%) was reported in subpopulations of two studies in China[112,128] and one study in the USA.[147] One of the studies in China included 2654 hospitalized patients with T2DM without ketosis (by definition, this subgroup would not have DKA)[112]; the other Chinese study included 508 patients with T2DM aged ≥65 years who received at least one dose of dapagliflozin and were followed for 24 weeks (the sample size and duration of follow-up may have contributed to the low prevalence in this study).[128] The US-based study included 32 White paediatric patients diagnosed with T2DM during the COVID-19 pandemic; the lack of DKA in these patients may be due to the small sample size, but the same study also found a DKA prevalence of 26% in 25 Black patients, suggesting disparity between racial groups.[147] The prevalence of DKA was 0.01%–37.5% in other study populations in the USA (42 publications)[14,19,21,23,24,29,31,32,62,65–67,78,79,82,90,91,108–110,117,118,123,130,136,138,140,143,145,146,150,151,153–157,163,165,166,168,172] and 0.01%–5.6% in European countries (17 publications).[33,40,51,56,89,101,116,126,127,135,139,144,149,152,159,162,175] The incidence of DKA was 0.55–9.1 per 1000 PY in the USA (13 publications)[18,19,29,47–49,77,143,149,150,152,158,159] and 0.001–19.8 per 1000 PY in European countries (5 publications).[56,89,101,175,179] There was no clear relationship between the number of patients included in each study and the incidence estimate, suggesting that major publication bias towards high incidence estimates in small studies is unlikely (Figure S1).

The prevalence and incidence of DKA also ranged widely in SGLT2i users. The prevalence in SGLT2i users was 0.0%–3.6% (5th–95th percentile: 0.02%–1.4%; 45 publications),[17,29,31,35,46,51,52,56,59,64,90,91,98,99,103,111,114,117–121,123,125,128,129,131,132,134,137,138,142,144,148,152–157,161,165,170,171,174] with two outliers of 15.4%[64] and 21.4%[17] (in 39 patients undergoing cardiac surgery[64] and 14 patients receiving canagliflozin,[17] respectively). The incidence of DKA in SGLT2i users was 0.0–9.1 events per 1000 PY (5th–95th percentile: 0.2–7.6 events per 1000 PY; 28 publications),[29,31,35,43,52,56,59,60,90,91,114,120,123,134,137,142,153–157,161,171,174,177,178,180,181] with an outlier of 24.5 events per 1000 PY (in 1087 patients undergoing emergency surgery).[60]

In insulin users, the prevalence of DKA was 0.1%–5.2% (11 publications),[21,32,56,89,110,123,126,127,134,141,146] with an outlier of 20.7% (in 58 Chinese patients)[141] and the incidence of DKA was 0.5–4.9 events per 1000 PY (3 publications).[56,89,123] The types of insulin used in these study populations were mostly mixed or unspecified (7 publications)[21,32,56,110,123,134,141]; single publications reported on patients using multiple daily injections or an insulin pump,[126] basal insulin,[127] insulin glargine,[146] and human insulin/neutral protamine Hagedorn or basal insulin analogue.[89]

Excluding newly diagnosed patients, the mean duration of T2DM was 0.6–18.4 years (30 publications),[12,21,25–27,35,54,56,58,59,68,69,77,78,86,89,93,97,111–113,128,129,131,135,141,144,153,161,183] whereas the median duration was 0.1–15 years (17 publications).[11,16,37,42,45,63,71,87,98,103,115,120,160,164,170,176,184] There was no clear relationship between the incidence of DKA and the mean or median duration of T2DM (Figure S2).

3.2 | Risk factors

3.2.1 | SGLT2i use

Many publications reported an increased risk (Figure 3, Table S5) or incidence (Figure S3) of DKA in SGLT2i users compared with non-users—this was not seen in all comparisons, likely due to small sample sizes in some studies.[29,31,35,42,43,51,56,59,60,64,90,91,123,125,134,143,153,154,178,185,186]

3.2.2 | Insulin use

Patients receiving insulin had numerically higher prevalence[56,123,134] and incidence[56,123] of DKA than those who did not receive insulin (Figures S4 and S5). The risk of DKA in patients using insulin was assessed in three large studies, each of which found an increased risk in users compared with non-users (odds ratio [OR] for hospitalization with a diagnosis of DKA = 1.8[118]; post-operative DKA incidence rate ratio [IRR] = 2.878[59]; DKA IRR [non-insulin vs. insulin] = 0.31[143]).

3.2.3 | Post hoc subgroup analyses

As the post hoc analyses were non-systematic, they are only briefly summarized here. Two publications showed that patients with a history of DKA/hyperglycaemic crises are at increased risk of DKA.[118,143] Patients with elevated glycated haemoglobin (five publications),[59,60,68,140,143] history of hypoglycaemia (two publications),[118,143] and uncontrolled T2DM (1 publication)[33] were also shown to be at increased risk of DKA. One of these publications reported a linear increase in risk of DKA with increasing

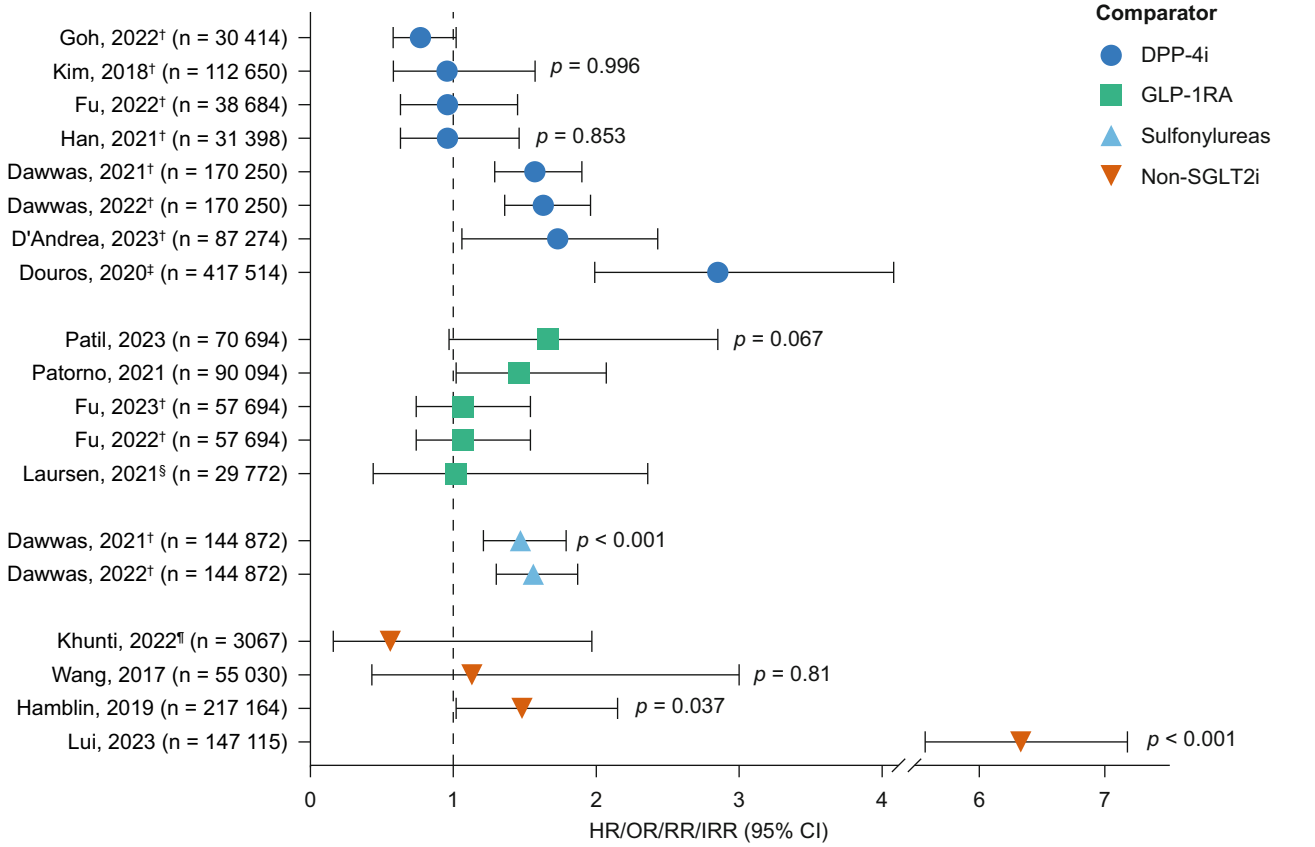

FIGURE 3 Risk of DKA in SGLT2i (mixed or unspecified type) users. Data shown are from studies that report risk associated with the SGLT2i class overall without specifying the type of SGLT2i (i.e., excluding publications that only reported use of specific types of SGLT2i: Canagliflozin, dapagliflozin, empagliflozin or sotagliflozin). Excludes an outlier: McCann, 2022,[64] who report OR = 38 (95% CI 9.1–158.7). Excludes Caparrotta, 2023[185] and McCoy, 2021,[143] who do not report the comparator. Excludes 2 publications that reported results for subgroups only: SGLT2i vs. non-SGLT2i in subgroups of patients undergoing emergency vs. elective operations,[60] and SGLT2i vs. DPP-4i in subgroups by data source (CCAE vs. MDCD vs. MDCR vs. Optum database).[90] †Propensity score-matched cohorts. ‡Adjusted for age (continuous), sex, diabetes duration (continuous) and deciles of time-conditional propensity score. §Adjusted for sex, age, diabetes duration, daily dose of insulin and year of becoming at risk. ¶Adjusted for age, sex, ethnicity, admission blood glucose level, insulin administration, and micro- and macrovascular disease. Data from D'Andrea, 2023,[29] Dawwas, 2022,[31] Dawwas, 2021,[178] Douros, 2020,[35] Fu, 2022,[186] Fu, 2023,[123] Goh, 2022,[125] Hamblin, 2019,[42] Han, 2021,[43] Khunti, 2022,[51] Kim, 2018,[134] Laursen, 2021,[56] Lui, 2023,[59] Patil, 2023,[153] Patorno, 2021,[154] and Wang, 2017.[91] CCAE, IBM MarketScan Commercial Claims and Encounters; CI, confidence interval; DKA, diabetic ketoacidosis; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; IRR, incidence rate ratio; MDCD, IBM MarketScan Multi-State Medicaid Database; MDCR, IBM MarketScan Medicare Supplemental and Coordination of Benefits; OR, odds ratio; RR, risk ratio; SGLT2i, sodium–glucose cotransporter-2 inhibitor.

blood glucose level (indicating increasingly poor glycaemic control).[143]

In two studies, Black race was associated with a higher prevalence of DKA than White race at the time of diagnosis of T2DM.[19,147] The incidence of DKA in patients with T2DM increased steadily with increasing age from 37 years onwards (1 study)[179]; analysis of the prevalence and incidence of DKA by age group across studies (based on study inclusion criteria) showed no consistent pattern (Table S6), perhaps owing to confounding. Two publications reported no association between body mass index/obesity and risk of DKA[33,59]; in a third publication (describing a paediatric study), body mass index z-score was significantly associated with DKA ($p = 0.004$).[140]

The prevalence of DKA in patients with CKD was 0.2%–0.7%[123,132,138] and the incidence was 2.5–4.9 events per 1000 PY.[123,180] Nephropathy was associated with DKA (IRR = 1.29) in a US analysis.[143] In another publication, renal failure was not a risk factor for DKA, whereas diabetes-related renal complications were associated with a reduced risk of DKA (OR = 0.31).[33] In short, the association of DKA with renal disease was inconclusive based on post hoc analysis of the published literature.

Among patients with newly diagnosed or new onset T2DM, 0.3%–50.0% presented with DKA (29 publications)[13,14,19,22–24,32,36,62,65–67,79,87,94,97,102,113,130,133,140,145,149,150,160,163,167,168,187]; the upper end of the range (50.0%) was from a study of patients with

ketosis-prone T2DM.[97] In two other studies of patients with ketosis-prone T2DM (new onset or previously diagnosed), the prevalence of DKA was 6.6%–30.2%.[36,113]

In a study of hospitalized patients with T2DM and ketosis, the prevalence of DKA was 12.1%.[112]

We found no data on the association between DKA and pregnancy, alcohol consumption, starvation or lactate level.

3.3 | Precipitating factors

Precipitating factors for DKA were reported in 31 publications.[11,16,17,25,37,42,45,48,52,54,58,69,71,73,75,77,80,83,86,88,93,95,113,131,188–194]

Infection (of any type) was the most common precipitating factor in 20 publications (65%).[16,17,25,37,42,54,58,69,71,75,77,86,88,93,95,113,189,190,192,194] Of the 20 publications, five had a study period that substantially overlapped with the COVID-19 pandemic[25,69,189,190] or was unknown.[88] One of these studies assessed the role of COVID-19 and found that infections were the precipitating factor for new-onset DKA in 30.5% and 36.4% of patients before and during the COVID-19 pandemic, respectively, with COVID-19 becoming the most common type of precipitating infection during the pandemic.[190]

Non-adherence to insulin was the precipitating factor for DKA in 10.5% of patients on average (range: 0.0%–23.4%; 7 publications),[11,17,58,69,71,75,86] and was less common as a precipitating factor than infection in all but one of the identified publications.[17,58,69,71,75,86] In the remaining publication, non-adherence to insulin and infection were equally common as precipitating factors.[11]

Non-compliance to any treatment (insulin or other medications) was the precipitating factor for DKA in 14.1% of patients on average (range: 0%–38.0%; 18 publications).[11,16,17,25,37,42,54,58,69,71,73,75,77,86,88,95,189,192]

Cardiovascular events were the precipitating factor for DKA in 5.8% of patients on average (range: 0.0%–13.5%; 4 publications)[69,71,80,95]; two publications specified acute coronary syndrome as a precipitating factor (in 5.4% and 12% of patients).[69,80]

More than half of the publications that reported precipitating factors for DKA (16/31) were unable to conclusively identify precipitating factors for some patients. The cause of DKA was unknown in 0.0%–51.1% of patients, suggesting an evidence gap in what triggers DKA.[11,17,25,37,42,48,54,58,69,71,73,75,88,95,188,192] On average, about 10% of patients had no obvious cause of DKA,[25,42,48,69,192] and in nearly a quarter of patients, the exact triggering factor was unknown.[11,17,37,48,54,58,71,73,75,88,95,188]

3.4 | Clinical burden

Overall mortality (due to DKA or other causes such as comorbidities) for patients with T2DM and DKA was reported in 46 publications and showed a wide range (Table 2).[11–13,16,17,25,32,37–42,47,49,51,54,55,59,61,63,68,69,71,72,74,77,86,88,90,92,93,95,96,100,104,109,115,124,179,182,189,192,194–196] Focusing on the large studies ($N > 2000$), without COVID-19 and not linked to the COVID-19 pandemic, gives a mortality of 1.0%–4.4%.[55,100,182,196]

Fifteen publications reported DKA-related complications.[11,12,25–27,37,49,69,71,73,81,92,95,179,196] Common complications occurring during/after DKA were acute kidney injury or failure (12.6%–64.3%; 4 publications),[69,81,95,196] hypokalaemia (12.3%–56%; 4 publications),[11,25,37,92] and arrhythmias (10.8%–28.6%; 2 publications).[69,95] In the largest of the 15 studies ($N = 19\,675$), the most common complication was acute kidney failure (42.9%).[196]

3.5 | Economic burden

Medical costs for DKA were reported in 8 publications (China, 3; Indonesia, 1; USA, 4; Table S7). Some publications noted that a high prevalence or severity of comorbidities in patients with T2DM and DKA may contribute to high costs.[100,196] In a study of hospitalized patients in China with T2DM and diabetic complications (DKA, coma, peripheral neuropathy, diabetic kidney disease, eye disorder, foot damage, cerebrovascular disease, cardiovascular disease and peripheral vascular disease), subgroups with and without DKA showed no difference in total hospitalization costs (median 7794.17 RMB with DKA vs. 8020.00 RMB without DKA), whereas the presence of ≥4 complications significantly increased costs (median 12177.62 RMB with ≥4 complications vs. 6349.72 RMB without complications).[106] In the USA, mean hospital costs for patients hospitalized with DKA were reported to be 36 000 USD[196] and 68 927 USD.[100] In a population covered under a Medicaid insurance plan, annual DKA hospital admission costs per plan member (averaged across all members with and without DKA hospital admissions) were estimated to be 500 USD in those using a FreeStyle Libre glucose monitoring system and 883 USD in those using blood glucose monitoring.[197]

The median length of hospital stay in patients hospitalized with DKA ranged from 65.1 h (~2.7 days) to 30.0 days (19 publications),[11,15,17,37,39,41,42,44,49,61,64,73,81,86,92,95,191,193,198] while the mean length of hospital stay was 2.2–24.6 days (13 publications).[12,16,47,59,69,71,77,88,93,100,179,196,199] In the USA, the length of stay ranged from 2.7 to 30.0 days (both median values).[39,44,81,100,196,199] Outside of the USA, the length of stay showed a similarly broad range, from 2.2 to 24.6 days (both mean values).[11,12,15–17,37,41,42,47,49,59,61,64,69,71,73,77,86,88,92,93,95,179,191,193,198] Overall, the shortest hospital stays were reported in youths admitted with isolated DKA (without severe hyperglycaemia or hyperosmolality)[81] and in adult patients treated with SGLT2is who had been diagnosed with T2DM ≥3 years before the admission with DKA and who had not received insulin treatment within 3 years of their diabetes diagnosis.[71] The longest hospital stays were reported in adult patients with COVID-19 being treated with a continuous insulin infusion for DKA[39] and in adult patients who had post-operative DKA after elective or emergency surgery without pre-operative SGLT2i treatment.[59]

TABLE 2 Summary of mortality in patients with T2DM and DKA.

Author, year	Subgroup	Sample size (*N*)	Mortality (%)
Large studies (*N* > 2000), without COVID-19 or related to the pandemic			
Bertasi, 2022[100]	N/A	153 475	4.4
Kumar, 2023[55]	N/A	2175	2.5
Sato, 2021[182]	N/A	13 835	4.3
Shaka, 2021[196]	N/A	19 675	1.0
Studies comparing subgroups[a]			
Almazrouei, 2023[11]	N/A	55	5.5
	SGLT2i	17	0.0
	Non-SGLT2i	38	7.9
Ata, 2021[17]	N/A	43	2.3
	SGLT2i (dapagliflozin)	31	3.2
	SGLT2i (empagliflozin)	9	0.0
	SGLT2i (canagliflozin)	3	0.0
Ata, 2023[16]	N/A	442	0.9
	New onset	176	1.1
	Pre-existing T2DM	266	0.8
Ebrahimi, 2022[179]	Male, 0–9 years	6	0.0
	Male, 10–19 years	9	0.0
	Male, 20–29 years	27	0.0
	Male, 30–59 years	416	2.6
	Male, 60–90 years	528	10.8
	Female, 0–9 years	5	0.0
	Female, 10–19 years	10	10.0
	Female, 20–29 years	17	0.0
	Female, 30–59 years	197	0.5
	Female, 60–90 years	482	9.8
Fan, 2023[115]	<20 years at diagnosis	NR	0.0
	20–39 years at diagnosis	NR	0.4
	≥40 years at diagnosis	NR	0.03
Fu, 2022[41]	DKA, acute pancreatitis	27	3.7
	No DKA, acute pancreatitis	109	0.0
Hamblin, 2019[42]	SGLT2i	37	5.4
	Non-SGLT2i	125	8.8
Kumar, 2023[55]	Hyperlactataemia	726	4.4
	Normolactataemia	1449	1.5
Lui, 2023[59]	SGLT2i	43	2.3
	Non-SGLT2i	339	11.5
Nakhleh, 2023[b]	SGLT2i	16	12.5
	Non-SGLT2i	55	20.0
Rashid, 2017[77]	N/A	128	12.5
	Known T2DM	118	13.6
	New onset	10	0.0
Wu, 2020[93]	N/A	65	0.0
	Hyperosmolar hyperglycaemia	19	5.3

(Continues)

TABLE 2 (Continued)

Author, year	Subgroup	Sample size (N)	Mortality (%)
Wang, 2019[90]	SGLT2i, CCAE database	218	0.0
	DPP-4i, CCAE database	171	0.0
	SGLT2i, MDCD database	32	3.1
	DPP-4i, MDCD database	76	1.3
	SGLT2i, MDCR database	37	2.7
	DPP-4i, MDCR database	57	3.5
Studies with COVID-19 or related to the pandemic			
Almistehi, 2021[104]	COVID-19	20	25.0
Dell'Aquila, 2023[32]	New onset, COVID-19	118	49.2
	Non-insulin dependent, COVID-19	29	27.6
Farzadfar, 2022[39]	COVID-19	50	62.0
	No COVID-19	50	4.0
Field, 2023[40]	Insulin, COVID-19	28	21.4
	No insulin, COVID-19	23	52.2
	COVID-19	57	36.8
	SGLT2i, COVID-19	6	33.3
Kempegowda, 2021[49]	COVID-19	15	26.7
	No COVID-19	2	0.0
	Pre-pandemic	8	0.0
Khunti, 2022[51]	COVID-19	86	33.7
	SGLT2i, COVID-19	7	28.6
	No SGLT2i, COVID-19	79	34.2
Misra, 2021[195]	Pandemic (Nov 2020–Feb 2021)	3912	19.2
	Pandemic (Mar–Jun 2020)	2831	17.1
	Pandemic (Jul–Oct 2020)	2613	11.6
	Pre-pandemic (Nov 2017–Feb 2020)	2608	10.7
	Pre-pandemic (Mar–Jun 2017–2019)	2010	10.2
	Pre-pandemic (Jul–Oct 2017–2019)	2011	8.9
Mondal, 2021[68]	COVID-19	26	11.5
Other studies			
Almazrouei, 2022[12]	N/A	48	6.3
Ameyaw, 2017[13]	N/A	16	0.0
Charoenpiriya, 2022[25]	N/A	53	0.0
Cymbaluk, 2021[109]	N/A	14	0.0
Eledrisi, 2022[37]	N/A	1011	7.4
Elkituni, 2021[38]	N/A	141	0.4
Gizaw, 2015[124]	N/A	16	6.3
Gnaneshwari, 2023[189]	N/A	30	10.0
Injinari, 2023[47]	N/A	11	18.2
Kruljac, 2018[54]	N/A	137	44.5
Ma, 2022[61]	N/A	136	0.7
Masuda, 2022[63]	N/A	73	1.4
Mondal, 2023[69]	N/A	37	8.1
Ndebele, 2018[192]	N/A	41	29.3
Nunes, 2021[c]	N/A	9	22.2
Patel, 2021[74]	N/A	26	61.5

TABLE 2 (Continued)

Author, year	Subgroup	Sample size (N)	Mortality (%)
Thewjitcharoen, 2019[86]	N/A	47	8.5
Tiwari, 2017[194]	N/A	50	4.0
Tomar, 2022[88]	N/A	23	4.3
Wong, 2016[92]	N/A	16	0.0
Xu, 2016[95]	N/A	294	3.4
Yo, 2014[96]	N/A	27	29.6

Abbreviations: CCAE, IBM MarketScan Commercial Claims and Encounters; COVID-19, coronavirus disease 2019; DKA, diabetic ketoacidosis; DPP-4i, dipeptidyl peptidase-4 inhibitor; MDCD, IBM MarketScan Multi-State Medicaid Database; MDCR, IBM MarketScan Medicare Supplemental and Coordination of Benefits; N/A, not applicable; NR, not reported; SGLT2i, sodium–glucose cotransporter-2 inhibitor; T2DM, type 2 diabetes mellitus.
[a]Non-treatment subgroups (e.g., by age, by sex) were defined after the protocol stage and were, therefore, not specified in the protocol or the DET. Data are added to the report where relevant, but this is a limitation of the SLR and some data for these subgroups may have been missed.
[b]See publication for long-term all-cause mortality.
[c]See publication for 2-year mortality.

3.6 | Humanistic burden

There is an evidence gap for information on humanistic burden from DKA. The one study identified suggested that a third of patients with DKA need 'total assistance' for daily living before being admitted to hospital (Figure S6); however, no details of the impact of DKA on health-related quality of life were reported.[182]

4 | DISCUSSION

Our SLR shows a high clinical burden of DKA in patients with T2DM. The included studies generally used a consistent definition of DKA, but DKA incidences ranged widely. Populations at increased risk of DKA included patients using SGLT2is, those using insulin and those with poor glycaemic control. The most common precipitating factors for DKA were infection (of any type) and non-adherence to treatment. Despite limited evidence on the impact of DKA on patients' health-related quality of life, the results highlight a high burden of complications. In addition, the length of hospital stay ranges from days to several weeks.

DKA has been considered an occasional complication of T2DM,[200] but our SLR results indicate that it occurs more frequently than has generally been perceived, especially in certain subgroups such as SGLT2i users. Consistent with our findings, two recent meta-analyses of real-world studies of patients with T2DM showed a significantly increased risk of DKA associated with the use of SGLT2is.[201,202] SGLT2is lower blood glucose by inhibiting glucose reabsorption in the kidneys.[203] The mechanisms underlying the increased risk of DKA in SGLT2i users are unclear, but dehydration and insulinopenia may contribute, with dehydration provoking increases in glucocorticoid and catecholamine concentrations, leading to adipose tissue lipolysis in the setting of insulinopenia.[204] Decreased insulin levels have also been suggested to divert hepatic free fatty acids towards beta-oxidation by increasing free fatty acid flux into the mitochondria via carnitine palmitoyltransferase 1.[205] The risk of DKA must be weighed against the benefits associated with SGLT2i use—as well as lowering blood glucose levels, SGLT2is have been shown to reduce cardiovascular risk in patients with T2DM.[206] SGLT2is (and/or glucagon-like peptide-1 receptor agonists) with demonstrated cardiovascular benefit are recommended by the ADA for patients with T2DM and established atherosclerotic cardiovascular disease or indicators of high atherosclerotic cardiovascular disease risk, heart failure or chronic kidney disease, with consideration of patient-specific factors.[207]

We also found good evidence that insulin users have a higher incidence of DKA than non-users. DKA in these patients may be caused by missed or inadequate doses of insulin.[8] Consistent with this, poor glycaemic control was identified as a risk factor for DKA in our SLR and an international consensus statement.[5] Insulin use may also signify more severe T2DM (with reduced endogenous insulin secretion) or longer disease duration, which may contribute to the increased risk of DKA in this group.[56,59]

The highest prevalence of DKA in our SLR (50.0%) was in a cohort with ketosis-prone T2DM.[97] A recent SLR by Kovacs et al. showed that ketosis-prone T2DM accounts for one third of DKA or ketosis cases at the onset of diabetes in adults.[208] Most of the studies in that SLR were conducted in Asian and African countries,[208] but one focused on a Caucasian population and found ketosis-prone T2DM in 23% of new-onset cases with ketosis,[209] indicating that ketosis-prone T2DM also needs to be considered in Caucasian patients.[208]

We found no clear relationship between the incidence of DKA and duration of T2DM. Limitations of these results include the reporting of T2DM duration as mean/median across studies and the presence of potential confounding factors. However, these results align with one publication that reported no significant difference in DKA incidence according to diabetes duration (mixed T1DM and T2DM)[38] and another publication reporting no significant effect of diabetes duration on the risk of post-operative DKA in SGLT2i users.[59]

Infection is a common trigger for DKA, as is non-adherence to treatment (insulin or other medications). Infection and omission or insufficient use of insulin therapy were also identified as common

triggers for DKA in an international consensus statement,[5] with infection being the most common precipitating factor worldwide. However, precipitating factors for DKA often remain unknown; more than half of the publications in this SLR that reported precipitating factors for DKA did not identify the trigger in some patients.

The length of stay in hospital with DKA varied widely in the studies included in our SLR. The greatest durations were reported in patient populations with other factors that likely contributed to the high length of stay (e.g., COVID-19 or surgical treatment). The shortest durations (median 2.7 days or mean 2.2 days) are close to the mean length of stay reported in an international consensus statement (3.7 days).[5]

While continuous glucose monitors have reduced the incidence of DKA,[126,127] there is still an unmet need for a convenient and reliable ketone monitoring tool. In 2021, a pilot study demonstrated the feasibility of continuous ketone monitoring.[7] Continuous glucose monitoring is already part of the ADA standards of care for patients treated with insulin and is widely available in many countries.[210] Combining continuous glucose and ketone monitoring in a single sensor would simplify the detection of ketone levels and reduce the risk of progression to full DKA.[3] In addition to patients receiving insulin, those with other risk factors such as SGLT2i treatment, recurrent infections or ketosis-prone T2DM may benefit. Further research may identify other subgroups that would benefit from continuous ketone monitoring.

Strengths of this SLR include its broad scope, systematic approach and large volume of data on DKA prevalence and incidence. A limitation is the variation in study designs, data sources, geographic locations (which may have differences in access to healthcare) and patient characteristics across the included studies. These differences may have contributed to the wide range of reported prevalence and incidence values for DKA. In addition, some publications reported prevalence and incidence for subgroups of patients (e.g., by treatment type), but not for the overall cohorts. These subgroups are included in the results, meaning that upper and lower bounds of ranges might be derived from specific subgroups that are at a higher and lower risk of DKA, respectively. Data for post hoc subgroups of interest were only extracted from publications in which data for the overall cohort were not reported. As such, data for post hoc subgroups were extracted and reported non-systematically and may be incomplete. The studies included in our SLR are unlikely to capture the incidence of mild/euglycemic DKA that occurs in routine clinical practice which is frequently missed. They are also unlikely to capture the incidence of DKA versus hyperglycaemic hyperosmolar state with ketosis, which may be difficult to distinguish. Socioeconomic risk factors for DKA (e.g., low income, area-level deprivation, housing insecurity, underinsurance or lack of insurance, and food insecurity[5]) were not a focus of this SLR. SGLT2i users were compared with four distinct control groups; evidence for each comparison is limited. The included studies were not assessed for quality or risk of bias in this broad-ranging SLR. There may be missing data in retrospective studies using medical charts, patients may be lost to follow-up in prospective studies, and interventional studies often have stringent eligibility criteria which may mean that the study population is not representative of the general population. The screening of references by a single reviewer may have introduced bias; however, checking of a sample of the title/abstract screening decisions by a second reviewer suggests this is unlikely.

DKA in T2DM has been generally overlooked and this is reflected in the identified evidence gaps. In many cases the cause of DKA was unknown, highlighting a level of uncertainty about the aetiology of DKA. In addition, the humanistic burden and costs associated with DKA were assessed in only a few identified studies. The results of our SLR provide a rationale for further research into the causes of DKA and its humanistic and economic burden in patients with T2DM.

In conclusion, our SLR provides an overview of the epidemiology of DKA and its implications in patients with T2DM. Our findings indicate a high clinical burden of DKA in these patients. Clinicians should therefore be alert to the possibility of DKA in patients with T2DM. Further research is needed to improve our understanding of DKA and its associated complications, identify high-risk patients and those with poor outcomes, and develop tools for convenient monitoring of ketones. This would allow for optimization of established treatments and early detection of ketone elevation, alleviating the burden of DKA in patients with T2DM and the healthcare system by preventing its onset altogether.

AUTHOR CONTRIBUTIONS

Carol Wysham, Anila Bindal and Yeesha Poon made substantial contributions to the conception and design and the analysis and interpretation of data; revised the manuscript critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Fleur Levrat-Guillen revised the manuscript critically for important intellectual content; gave final approval of the version to be published; and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Desislava Kostadinova made substantial contributions to the acquisition, analysis and interpretation of data; was involved in drafting the manuscript; gave final approval of the version to be published; and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

ACKNOWLEDGEMENTS

Medical writing support was provided by Dr. Claire Mulligan (Beacon Medical Communications Ltd., Brighton, UK) in accordance with Good Publication Practice (GPP 2022) guidelines and was funded by Abbott.

FUNDING INFORMATION

This study was funded by Abbott.

CONFLICT OF INTEREST STATEMENT

Carol Wysham has received research funding from Abbott, AbbVie, Bayer, Eli Lilly and Company, and Novo Nordisk, and has served as a speaker/advisor for Abbott, Biomea, Eli Lilly and Company, MannKind, and Novo Nordisk. Anila Bindal, Fleur Levrat-Guillen and Yeesha Poon are employees of Abbott. Desislava Kostadinova is an employee of Oxford PharmaGenesis, which received funding from Abbott to conduct the SLR.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

ORCID

Carol Wysham https://orcid.org/0000-0002-3056-0047
Yeesha Poon https://orcid.org/0000-0002-4290-832X

REFERENCES

1. International Diabetes Federation. IDF Diabetes Atlas. 2021. https://diabetesatlas.org/. Accessed March, 2024.
2. World Health Organization. Diabetes. Key facts. 2023. https://www.who.int/news-room/fact-sheets/detail/diabetes. Accessed March, 2024.
3. Virdi N, Poon Y, Abaniel R, Bergenstal RM. Prevalence, cost, and burden of diabetic ketoacidosis. *Diabetes Technol Ther*. 2023;25(S3):S75-S84.
4. Lizzo JM, Goyal A, Gupta V. *Adult Diabetic Ketoacidosis*. StatPearls; 2024.
5. Umpierrez GE, Davis GM, ElSayed NA, et al. Hyperglycemic crises in adults with diabetes: a consensus report. *Diabetes Care*. 2024;47(8):1257-1275.
6. Nguyen KT, Xu NY, Zhang JY, et al. Continuous ketone monitoring consensus report 2021. *J Diabetes Sci Technol*. 2022;16(3):689-715.
7. Alva S, Castorino K, Cho H, Ou J. Feasibility of continuous ketone monitoring in subcutaneous tissue using a ketone sensor. *J Diabetes Sci Technol*. 2021;15(4):768-774.
8. American Diabetes Association Professional Practice Committee. 2. Diagnosis and classification of diabetes: standards of Care in Diabetes-2024. *Diabetes Care*. 2024;47(Suppl 1):S20-S42.
9. Abate MD, Semachew A, Emishaw S, et al. Incidence and predictors of hyperglycemic emergencies among adult diabetic patients in Bahir Dar city public hospitals, Northwest Ethiopia, 2021: a multicenter retrospective follow-up study. *Front Public Health*. 2023;11:1116713.
10. Agboghoroma OF, Jobe M, Forrest K. Clinical characteristics of people with diabetic ketoacidosis at a clinic in The Gambia: a retrospective study. *J Endocrinol Metab Diabetes S Afr*. 2022;28(1):14-17.
11. Almazrouei R, Afandi B, AlKindi F, Govender R, Al-Shamsi S. Clinical characteristics and outcomes of diabetic ketoacidosis in patients with type 2 diabetes using SGLT2 inhibitors. *Clin Med Insights Endocrinol Diabetes*. 2023;16:11795514231153717.
12. Almazrouei R, Siddiqua AR, Alnuaimi M, Al-Shamsi S, Govender R. Clinical and biochemical characteristics of diabetic ketoacidosis in adults with type 1 or type 2 diabetes at a tertiary hospital in The United Arab Emirates. *Front Clin Diabetes Healthc*. 2022;3:918253.
13. Ameyaw E, Asafo-Agyei SB, Thavapalan S, Middlehurst AC, Ogle GD. Clinical profile of diabetes at diagnosis among children and adolescents at an endocrine clinic in Ghana. *World J Diabetes*. 2017;8(9):429-435.
14. Astudillo M, Tosur M, Castillo B, et al. Type 2 diabetes in prepubertal children. *Pediatr Diabetes*. 2021;22(7):946-950.
15. Ata F, Khan AA, Khamees I, et al. Clinical and biochemical determinants of length of stay, readmission and recurrence in patients admitted with diabetic ketoacidosis. *Ann Med*. 2023;55(1):533-542.
16. Ata F, Khan AA, Khamees I, et al. Differential evolution of diabetic ketoacidosis in adults with pre-existent versus newly diagnosed type 1 and type 2 diabetes mellitus. *BMC Endocr Disord*. 2023;23(1):193.
17. Ata F, Yousaf Z, Khan AA, et al. SGLT-2 inhibitors associated euglycemic and hyperglycemic DKA in a multicentric cohort. *Sci Rep*. 2021;11(1):10293.
18. Ata F, Khan AA, Khamees I, Bashir M. Incidence of diabetic ketoacidosis does not differ in Ramadan compared to other months and seasons: results from a 6-year multicenter study. *Curr Med Res Opin*. 2023;39(8):1061-1067.
19. Bacha F, Cheng P, Gal RL, et al. Racial and ethnic disparities in comorbidities in youth with type 2 diabetes in the pediatric diabetes consortium (PDC). *Diabetes Care*. 2021;44(10):2245-2251.
20. Batra N, Garg H, Singh G, Mujral A. Macrovascular and microvascular complications in newly diagnosed type 2 diabetes mellitus. *Indian J Public Health Res Dev*. 2022;13(3):199-204.
21. Beck SE, Kelly C, Price DA, Group CS. Non-adjunctive continuous glucose monitoring for control of hypoglycaemia (COACH): results of a post-approval observational study. *Diabet Med*. 2022;39(2):e14739.
22. Braham R, Alzaid A, Robert AA, et al. Double diabetes in Saudi Arabia: a new entity or an underestimated condition. *World J Diabetes*. 2016;7(20):621-626.
23. Chambers MA, Mecham C, Arreola EV, Sinha M. Increase in the number of pediatric new-onset diabetes and diabetic ketoacidosis cases during the COVID-19 pandemic. *Endocr Pract*. 2022;28(5):479-485.
24. Chao LC, Vidmar AP, Georgia S. Spike in diabetic ketoacidosis rates in pediatric type 2 diabetes during the COVID-19 pandemic. *Diabetes Care*. 2021;44(6):1451-1453.
25. Charoenpiriya A, Chailurkit L, Ongphiphadhanakul B. Comparisons of biochemical parameters and diabetic ketoacidosis severity in adult patients with type 1 and type 2 diabetes. *BMC Endocr Disord*. 2022;22(1):7.
26. Chen YL, Weng SF, Yang CY, Wang JJ, Tien KJ. Long-term risk of stroke in type 2 diabetes patients with diabetic ketoacidosis: a population-based, propensity score-matched, longitudinal follow-up study. *Diabetes Metab*. 2017;43(3):223-228.
27. Chen YL, Weng SF, Yang CY, Wang JJ, Tien KJ. Diabetic ketoacidosis further increases risk of Alzheimer's disease in patients with type 2 diabetes. *Diabetes Res Clin Pract*. 2019;147:55-61.
28. Dabelea D, Rewers A, Stafford JM, et al. Trends in the prevalence of ketoacidosis at diabetes diagnosis: the search for diabetes in youth study. *Pediatrics*. 2014;133(4):e938-e945.
29. D'Andrea E, Wexler DJ, Kim SC, Paik JM, Alt E, Patorno E. Comparing effectiveness and safety of SGLT2 inhibitors vs DPP-4 inhibitors in patients with type 2 diabetes and varying baseline HbA1c levels. *JAMA Intern Med*. 2023;183(3):242-254.
30. Davis TME, Davis W. Incidence and associates of diabetic ketoacidosis in a community-based cohort: the Fremantle diabetes study phase II. *BMJ Open Diabetes Res Care*. 2020;8(1):e000983.
31. Dawwas GK, Flory JH, Hennessy S, Leonard CE, Lewis JD. Comparative safety of sodium-glucose cotransporter 2 inhibitors versus dipeptidyl peptidase 4 inhibitors and sulfonylureas on the risk of diabetic ketoacidosis. *Diabetes Care*. 2022;45(4):919-927.
32. Dell'Aquila K, Lee J, Wang SH, et al. Incidence, characteristics, risk factors and outcomes of diabetic ketoacidosis in COVID-19 patients: comparison with influenza and pre-pandemic data. *Diabetes Obes Metab*. 2023;25(9):2482-2494.
33. Di Giovanni P, Meo F, Cedrone F, et al. Predictors and trend of ketoacidosis hospitalization rate in type 2 diabetes mellitus patients

from 2006 to 2015 in Abruzzo region, Italy. *Clin Ter*. 2020;170(1): e53-e58.
34. Dong W, Zhang S, Yan S, Zhao Z, Zhang Z, Gu W. Clinical characteristics of patients with early-onset diabetes mellitus: a single-center retrospective study. *BMC Endocr Disord*. 2023;23(1):216.
35. Douros A, Lix LM, Fralick M, et al. Sodium-glucose Cotransporter-2 inhibitors and the risk for diabetic ketoacidosis: a multicenter cohort study. *Ann Intern Med*. 2020;173(6):417-425.
36. Du S, Zhang H, Wu H, Ye S, Li W, Su Q. Prevalence and gender differences of metabolic syndrome in young ketosis-prone type 2 diabetic individuals: a retrospective study. *Diabetes Metab Syndr Obes*. 2020;13:2719-2727.
37. Eledrisi MS, Alkabbani H, Aboawon M, et al. Clinical characteristics and outcomes of care in patients hospitalized with diabetic ketoacidosis. *Diabetes Res Clin Pract*. 2022;192:110041.
38. Elkituni A, Elshwekh H, Bendala NM, Atwear WS, Aldaba FA, Fellah AM. Profile of diabetic ketoacidosis at the National Diabetes and endocrine Center in Tripoli, Libya, 2015. *Diabetes Metab Syndr*. 2021;15(3):771-775.
39. Farzadfar D, Gordon CA, Falsetta KP, et al. Assessment of insulin infusion requirements in COVID-19-infected patients with diabetic ketoacidosis. *Endocr Pract*. 2022;28(8):787-794.
40. Field BCT, Ruan Y, Varnai KA, et al. A UK nationwide study of adults admitted to hospital with diabetic ketoacidosis or hyperosmolar hyperglycaemic state and COVID-19. *Diabetes Obes Metab*. 2023; 25(7):2012-2022.
41. Fu Y, Liu X, Cui B, Wang C, Liu Z, Zhao B. Clinical characteristics of concomitant diabetic ketoacidosis in type 2 diabetes patients with acute pancreatitis. *Diabetes Metab Syndr Obes*. 2022;15:111-119.
42. Hamblin PS, Wong R, Ekinci EI, et al. SGLT2 inhibitors increase the risk of diabetic ketoacidosis developing in the community and during hospital admission. *J Clin Endocrinol Metab*. 2019;104(8):3077-3087.
43. Han SJ, Ha KH, Lee N, Kim DJ. Effectiveness and safety of sodium-glucose co-transporter-2 inhibitors compared with dipeptidyl peptidase-4 inhibitors in older adults with type 2 diabetes: a nationwide population-based study. *Diabetes Obes Metab*. 2021;23(3): 682-691.
44. Hao S, Cossen K, Westbrook AL, Umpierrez GE, Vellanki P. Diabetic ketoacidosis and Long-term insulin requirements in youths with newly diagnosed type 2 diabetes during the SARS-CoV-2 pandemic. *Endocr Pract*. 2023;29(10):754-761.
45. Hirobata T, Inaba H, Kaido Y, et al. Serum ketone body measurement in patients with diabetic ketoacidosis. *Diabetol Int*. 2022;13(4): 624-630.
46. Hitchen SA, Lan NSR, Rankin JM, Larbalestier R, Yeap BB, Fegan PG. Real-world barriers and safety of initiating sodium-glucose co-transporter 2 inhibitor treatment immediately following an acute cardiac event in people with diabetes. *J Diabetes Complications*. 2021;35(12):108057.
47. Injinari N, Ghoshouni H, Mehrabbeik A, Namiranian N, Ghadiri-Anari A, Azizi R. Comparison of diabetic ketoacidosis characteristics during- and before the COVID-19 pandemic. *Int J Endocrinol Metab*. 2023;21(3):e134882.
48. Kamata Y, Takano K, Kishihara E, Watanabe M, Ichikawa R, Shichiri M. Distinct clinical characteristics and therapeutic modalities for diabetic ketoacidosis in type 1 and type 2 diabetes mellitus. *J Diabetes Complications*. 2017;31(2):468-472.
49. Kempegowda P, Melson E, Johnson A, et al. Effect of COVID-19 on the clinical course of diabetic ketoacidosis (DKA) in people with type 1 and type 2 diabetes. *Endocr Connect*. 2021;10(4):371-377.
50. Khan AA, Ata F, Bashir M, Iqbal P, Kartha A. Clinical and biochemical predictors of intensive care unit admission among patients with diabetic ketoacidosis. *World J Diabetes*. 2023;14(3):271-278.
51. Khunti K, Ruan Y, Davies J, et al. Association between SGLT2 inhibitor treatment and diabetic ketoacidosis and mortality in people with type 2 diabetes admitted to hospital with COVID-19. *Diabetes Care*. 2022;45(12):2838-2843.
52. Kohler S, Salsali A, Hantel S, et al. Safety and tolerability of empagliflozin in patients with type 2 diabetes. *Clin Ther*. 2016;38(6):1299-1313.
53. Korsa AT, Genemo ES, Bayisa HG, Dedefo MG. Diabetes mellitus complications and associated factors among adult diabetic patients in selected hospitals of West Ethiopia. *Open Cardiovasc Med J*. 2019; 13(1):41-48.
54. Kruljac I, Cacic M, Cacic P, et al. All-cause mortality prognostic factors in type 2 diabetes-associated ketosis and ketoacidosis. *Endocr Oncol Metab*. 2018;4(1):12-22.
55. Kumar A, Doola R, Zahumensky A, et al. Association between elevated lactate and clinical outcomes in adults with diabetic ketoacidosis. *J Crit Care*. 2023;78:154377.
56. Laursen HVB, Roikjer JB, Dal J, Jensen MH. Sodium glucose Cotransporter-2 inhibitor treatment and the risk of diabetic ketoacidosis in Denmark: a retrospective cohort study of five years of use. *Curr Drug Saf*. 2021;16(1):73-81.
57. Li L, Li L. Risk factors for diabetic ketoacidosis in acute pancreatitis patients with type 2 diabetes. *BMC Gastroenterol*. 2023;23(1):257.
58. Łoś A, Wójcik-Odyniec J, Sobol-Pacyniak A, Cypryk K. Diabetic ketoacidosis as a reason for hospitalization in adult patients with any type of diabetes mellitus. *Clin Diabetol*. 2018;7(5):215-221.
59. Lui DTW, Wu T, Au ICH, et al. A population-based study of SGLT2 inhibitor-associated postoperative diabetic ketoacidosis in patients with type 2 diabetes. *Drug Saf*. 2023;46(1):53-64.
60. Lui DTW, Wu T, Liu X, et al. 860-P: a territory-wide study of SGLT2 inhibitor–associated postoperative diabetic ketoacidosis in type 2 diabetes patients. *Diabetes*. 2022;71(Suppl 1):860–P.
61. Ma LP, Liu X, Cui BC, Liu Y, Wang C, Zhao B. Diabetic ketoacidosis with acute pancreatitis in patients with type 2 diabetes in the emergency department: a retrospective study. *Front Med Lausanne*. 2022; 9:813083.
62. Marks BE, Khilnani A, Meyers A, et al. Increase in the diagnosis and severity of presentation of pediatric type 1 and type 2 diabetes during the COVID-19 pandemic. *Horm Res Paediatr*. 2021;94(7–8): 275-284.
63. Masuda S, Ota K, Okazaki R, et al. Clinical characteristics associated with the development of diabetic ketoacidosis in patients with type 2 diabetes. *Intern Med*. 2022;61(8):1125-1132.
64. McCann M, O'Brien A, Larbalestier R, Davis T. Sodium-glucose cotransport-2 inhibitor induced ketoacidosis following coronary artery bypass surgery: implications for management. *Intern Med J*. 2022;52(5):876-879.
65. McIntyre T, Sarah S, Benjamin R, Balikcioglu PG. Disrupted pediatric diabetes trends in the second year of the COVID-19 pandemic. *J Endocr Soc*. 2023;7(8):bvad092.
66. Miller A, Joseph S, Badran A, Umpaichitra V, Bargman R, Chin VL. Increased rates of hospitalized children with type 1 and type 2 diabetes mellitus in Central Brooklyn during the COVID-19 pandemic. *Int J Pediatr*. 2023;2023:4580809.
67. Modarelli R, Sarah S, Ramaker ME, Bolobiongo M, Benjamin R, Gumus Balikcioglu P. Pediatric diabetes on the rise: trends in incident diabetes during the COVID-19 pandemic. *J Endocr Soc*. 2022; 6(4):bvac024.
68. Mondal S, DasGupta R, Lodh M, et al. Predictors of new-onset diabetic ketoacidosis in patients with moderate to severe COVID-19 receiving parenteral glucocorticoids: a prospective single-centre study among Indian type 2 diabetes patients. *Diabetes Metab Syndr*. 2021;15(3):795-801.
69. Mondal S, DasGupta R, Lodh M, Parida A, Haldar M, Ganguly A. Diabetic keto-acidosis in pancreatic diabetes – how is it different from DKA in type 1 or type 2 DM? *Int J Diabetes Dev Ctries*. 2023;44(2): 278-288.

70. Nabi T, Rafiq N, Rahman MHU, Rasool S, Wani NUD. Comparative study of emphysematous pyelonephritis and pyelonephritis in type 2 diabetes: a single-centre experience. *J Diabetes Metab Disord*. 2020;19(2):1273-1282.
71. Nakhleh A, Othman A, Masri A, Zloczower M, Zolotov S, Shehadeh N. Clinical outcomes of diabetic ketoacidosis in type 2 diabetes patients with and without SGLT2 inhibitor treatment: a retrospective study. *Biomedicine*. 2023;11(10):01.
72. Nunes RTL, Mota C, Lins PRG, et al. Incidence, characteristics and long-term outcomes of patients with diabetic ketoacidosis: a prospective prognosis cohort study in an emergency department. *Sao Paulo Med J*. 2021;139(1):10-17.
73. Ooi E, Nash K, Rengarajan L, et al. Clinical and biochemical profile of 786 sequential episodes of diabetic ketoacidosis in adults with type 1 and type 2 diabetes mellitus. *BMJ Open Diabetes Res Care*. 2021;9(2):e002451.
74. Patel U, Deluxe L, Salama C, et al. Evaluation of characteristics and outcomes for patients with diabetic ketoacidosis (DKA) with and without COVID-19 in Elmhurst Queens during similar three-month periods in 2019 and 2020. *Cureus*. 2021;13(7):e16427.
75. Prajapati BK. Clinical profile of diabetic ketoacidosis in adults in Dhulikhel hospital. *Kathmandu Univ Med J*. 2017;15(57):25-28.
76. Praveen PA, Hockett CW, Ong TC, et al. Diabetic ketoacidosis at diagnosis among youth with type 1 and type 2 diabetes: results from SEARCH (United States) and YDR (India) registries. *Pediatr Diabetes*. 2021;22(1):40-46.
77. Rashid MO, Sheikh A, Salam A, Farooq S, Kiran Z, Islam N. Diabetic ketoacidosis characteristics and differences in type 1 versus type 2 diabetes patients. *J Ayub Med Coll Abbottabad*. 2017;29(3):398-402.
78. Reid LA, Mendoza JA, Merchant AT, et al. Household food insecurity is associated with diabetic ketoacidosis but not severe hypoglycemia or glycemic control in youth and young adults with youth-onset type 2 diabetes. *Pediatr Diabetes*. 2022;23(7):982-990.
79. Rodriguez BC, Astudillo M, Tosur M, et al. Characteristics of type 2 diabetes in female and male youth. *Clin Diabetes*. 2023;41(2):239-243.
80. Saadeh NA, Hammouri HM, Zahran DJ. Diabetic ketoacidosis in northern Jordan: seasonal morbidity and characteristics of patients. *Diabetes Metab Syndr Obes*. 2023;16:3057-3064.
81. Schmitt J, Rahman AF, Ashraf A. Concurrent diabetic ketoacidosis with hyperosmolality and/or severe hyperglycemia in youth with type 2 diabetes. *Endocrinol Diabetes Metab*. 2020;3(3):e00160.
82. Stevens JS, Bogun MM, McMahon DJ, et al. Diabetic ketoacidosis and mortality in COVID-19 infection. *Diabetes Metab*. 2021;47(6):101267.
83. Takai T, Okada Y, Takebe R, Nakamura T. Vomiting and hyperkalemia are novel clues for emergency room diagnosis of type 1 diabetic ketoacidosis: a retrospective comparison between diabetes types. *Diabetol Int*. 2022;13(1):272-279.
84. Takeuchi M, Kawamura T, Sato I, Kawakami K. Population-based incidence of diabetic ketoacidosis in type 2 diabetes: medical claims data analysis in Japan. *Pharmacoepidemiol Drug Saf*. 2018;27(1):123-126.
85. Thammakosol K, Sriphrapradang C. Effectiveness and safety of early insulin glargine administration in combination with continuous intravenous insulin infusion in the management of diabetic ketoacidosis: a randomized controlled trial. *Diabetes Obes Metab*. 2023;25(3):815-822.
86. Thewjitcharoen Y, Plianpan P, Chotjirat A, et al. Clinical characteristics and outcomes of care in adult patients with diabetic ketoacidosis: a retrospective study from a tertiary diabetes center in Thailand. *J Clin Transl Endocrinol*. 2019;16:100188.
87. Tittel SR, Laubner K, Schmid SM, et al. Immune-checkpoint inhibitor-associated diabetes compared to other diabetes types - a prospective, matched control study. *J Diabetes*. 2021;13(12):1007-1014.
88. Tomar MS, Katariya D, Charel K. To study clinical and bio chemical parameters of diabetic keto acidosis patients. *Int J Toxicol Pharmacol Res*. 2022;12(6):102-108.
89. van Mark G, Tittel SR, Welp R, et al. DIVE/DPV registries: benefits and risks of analog insulin use in individuals 75 years and older with type 2 diabetes mellitus. *BMJ Open Diabetes Res Care*. 2021;9(1):e002215.
90. Wang L, Voss EA, Weaver J, et al. Diabetic ketoacidosis in patients with type 2 diabetes treated with sodium glucose co-transporter 2 inhibitors versus other antihyperglycemic agents: an observational study of four US administrative claims databases. *Pharmacoepidemiol Drug Saf*. 2019;28(12):1620-1628.
91. Wang Y, Desai M, Ryan PB, et al. Incidence of diabetic ketoacidosis among patients with type 2 diabetes mellitus treated with SGLT2 inhibitors and other antihyperglycemic agents. *Diabetes Res Clin Pract*. 2017;128:83-90.
92. Wong B, Cheng A, Yu C, Goguen J. Examining the "killer K" of diabetic ketoacidosis at a tertiary care hospital: an exploratory study. *Can J Diabetes*. 2016;40(3):204-209.
93. Wu XY, She DM, Wang F, et al. Clinical profiles, outcomes and risk factors among type 2 diabetic inpatients with diabetic ketoacidosis and hyperglycemic hyperosmolar state: a hospital-based analysis over a 6-year period. *BMC Endocr Disord*. 2020;20(1):182.
94. Xiong X, Wei L, Xiao Y, et al. Effects of family history of diabetes on pancreatic beta-cell function and diabetic ketoacidosis in newly diagnosed patients with type 2 diabetes: a cross-sectional study in China. *BMJ Open*. 2021;11(1):e041072.
95. Xu Y, Bai J, Wang G, et al. Clinical profile of diabetic ketoacidosis in tertiary hospitals in China: a multicentre, clinic-based study. *Diabet Med*. 2016;33(2):261-268.
96. Yo CH, Lee MT, Gi WT, et al. Prognostic determinants of community-acquired bloodstream infection in type 2 diabetic patients in ED. *Am J Emerg Med*. 2014;32(12):1450-1454.
97. Zhang M, Li Y, Cui W, et al. The clinical and metabolic characteristics of young-onset ketosis-prone type 2 diabetes in China. *Endocr Pract*. 2015;21(12):1364-1371.
98. Zhao Q, Tan Y, Wu Q, et al. The risk factors of diabetic ketosis and diabetic ketoacidosis among patients with type 2 diabetes mellitus treated with SGLT2 inhibitors: a retrospective study. *Expert Opin Drug Saf*. 2024;23(1):57-65.
99. Zhao Z, Zhao F, Zhang Y, et al. Risk factors of dapagliflozin-associated diabetic ketosis/ketoacidosis in patients with type 2 diabetes mellitus: a matched case-control study. *Diabetes Res Clin Pract*. 2023;196:110236.
100. Bertasi T, Aguilar-Gallardo JS, Bilani N, Garcia ME, Fermin DM, Bertasi R. Characteristics and hospital outcomes of patients with type 1 and type 2 diabetes hospitalized with diabetic ketoacidosis in the United States. *J Gen Intern Med*. 2022;37(Suppl. 2):S177.
101. Roussel R, Riveline JP, Vicaut E, et al. Important drop in rate of acute diabetes complications in people with type 1 or type 2 diabetes after initiation of flash glucose monitoring in France: the RELIEF study. *Diabetes Care*. 2021;44(6):1368-1376.
102. Agathis NT, Womack LS, Webber BJ, et al. Children, adolescents, and young adults hospitalized with COVID-19 and diabetes in summer 2021. *Pediatr Diabetes*. 2022;23(7):961-967.
103. Alguwaihes AM. Safety of dapagliflozin in patients with type 2 diabetes mellitus in Saudi Arabia: a post authorization safety study. *Diabetes Ther*. 2021;12(7):1979-1992.
104. Almistehi WM, Alturki AM, Bukhari BA. Incidence of diabetic ketoacidosis in hospitalized COVID19 patients with type 2 diabetes. *J Endocrinol Soc*. 2021;5(Suppl 1):A346-A347.
105. Annani-Akollor ME, Addai-Mensah O, Fondjo LA, et al. Predominant complications of type 2 diabetes in Kumasi: a 4-year retrospective

cross-sectional study at a teaching Hospital in Ghana. *Medicina*. 2019;55(5):125. doi:10.3390/medicina55050125
106. Bao X, Yang C, Fang K, Shi M, Yu G, Hu Y. Hospitalization costs and complications in hospitalized patients with type 2 diabetes mellitus in Beijing, China. *J Diabetes*. 2017;9(4):405-411.
107. Bedaso A, Oltaye Z, Geja E, Ayalew M. Diabetic ketoacidosis among adult patients with diabetes mellitus admitted to emergency unit of Hawassa university comprehensive specialized hospital. *BMC Res Notes*. 2019;12(1):137.
108. Chao C, Andrade SB, Bergford S, et al. Assessing non-adjunctive CGM safety at home and in new markets (ANSHIN). *Endocrinol Diabetes Metab*. 2023;6(3):e414.
109. Cymbaluk A, Astudillo M, Desalvo D, Bacha F, McKay S, Redondo MJ. 901-P: COVID-19 and type 2 diabetes: children spared from severe disease course. *Diabetes*. 2021;70(Suppl 1):901-P.
110. Davis KL, Wei W, Meyers JL, Kilpatrick BS, Pandya N. Association between different hemoglobin A1c levels and clinical outcomes among elderly nursing home residents with type 2 diabetes mellitus. *J Am Med Dir Assoc*. 2014;15(10):757-762.
111. Dissanayake H, Dilrukshi S, Ratnasamy V, et al. Empagliflozin in south Asians with type 2 diabetes: real world data on effects on cardiometabolic parameters, safety and determinants of response to therapy from a diabetes practice in Sri Lanka. *Prim Care Diabetes*. 2023;17(1):98-104.
112. Du S, Yang X, Shi D, Su Q. Characteristics of type 2 diabetes with ketosis in Baoshan, Yunnan of China. *J Diabetes Res*. 2016;2016:7854294.
113. Du S, Yang X, Shi D, Su Q. Comparison between new-onset and old-diagnosed type 2 diabetes with ketosis in rural regions of China. *Int J Endocrinol*. 2016;2016:3010243.
114. Erondu N, Desai M, Ways K, Meininger G. Diabetic ketoacidosis and related events in the canagliflozin type 2 diabetes clinical program. *Diabetes Care*. 2015;38(9):1680-1686.
115. Fan Y, Lau ESH, Wu H, et al. Incident cardiovascular-kidney disease, diabetic ketoacidosis, hypoglycaemia and mortality in adult-onset type 1 diabetes: a population-based retrospective cohort study in Hong Kong. *Lancet Reg Health West Pac*. 2023;34:100730.
116. Fernandez-Planelles MC, Palazon-Bru A, Calvo-Perez M, Pico-Alfonso AM, Gil-Guillen VF. Impact of a clinical pathway on cardiovascular risk in patients with diabetes. *Postgrad Med*. 2022;134(1):96-103.
117. Fralick M, Kulldorff M, Redelmeier D, et al. A novel data mining application to detect safety signals for newly approved medications in routine care of patients with diabetes. *Endocrinol Diabetes Metab*. 2021;4(3):e00237.
118. Fralick M, Redelmeier DA, Patorno E, et al. Identifying risk factors for diabetic ketoacidosis associated with SGLT2 inhibitors: a Nationwide cohort study in the USA. *J Gen Intern Med*. 2021;36(9):2601-2607.
119. Bhatt DL, Szarek M, Pitt B, et al. Sotagliflozin in patients with diabetes and chronic kidney disease. *N Engl J Med*. 2021;384(2):129-139.
120. Cahn A, Mosenzon O, Wiviott SD, et al. Efficacy and safety of dapagliflozin in the elderly: analysis from the DECLARE-TIMI 58 study. *Diabetes Care*. 2020;43(2):468-475.
121. Chiang B, Chew DP, De Pasquale CG. Outcome trial data on sodium glucose cotransporter-2 inhibitors: putting clinical benefits and risks in perspective. *Int J Cardiol*. 2022;349:96-98.
122. Ferrannini E, Baldi S, Frias JP, et al. Hormone-substrate changes with exenatide plus dapagliflozin versus each drug alone: the randomized, active-controlled DURATION-8 study. *Diabetes Obes Metab*. 2020;22(1):99-106.
123. Fu EL, D'Andrea E, Wexler DJ, Patorno E, Paik JM. Safety of sodium-glucose Cotransporter-2 inhibitors in patients with CKD and type 2 diabetes: population-based US cohort study. *Clin J Am Soc Nephrol*. 2023;18(5):592-601.
124. Gizaw M, Harries AD, Ade S, et al. Diabetes mellitus in Addis Ababa, Ethiopia: admissions, complications and outcomes in a large referral hospital. *Public Health Action*. 2015;5(1):74-78.
125. Goh LGH, Sun J, Ong BSK, Khoo D, Sum CF, Ng K. Real-world evaluation of sodium-glucose co-transporter-2 inhibitors and dipeptidyl peptidase-4 inhibitors for managing type 2 diabetes mellitus: a retrospective multi-ethnic cohort study. *J Diabetes Metab Disord*. 2022;21(1):521-555.
126. Guerci B, Levrat-Guillen F, Vicaut E, et al. Reduced acute diabetes events after FreeStyle libre system initiation in people 65 years or older with type 2 diabetes on intensive insulin therapy in France. *Diabetes Technol Ther*. 2023;25(6):384-394.
127. Guerci B, Roussel R, Levrat-Guillen F, et al. Important decrease in hospitalizations for acute diabetes events following FreeStyle libre system initiation in people with type 2 diabetes on basal insulin therapy in France. *Diabetes Technol Ther*. 2023;25(1):20-30.
128. Guo L, Wang J, Li L, et al. Real-world safety of dapagliflozin in elderly patients with type 2 diabetes in China: post-hoc analysis of the DONATE study. *Diabetologia*. 2022;65(Suppl 1):S278-S279.
129. Guo L, Wang J, Li L, et al. A multicentre, prospective, non-interventional study evaluating the safety of dapagliflozin in patients with type 2 diabetes in routine clinical practice in China (DONATE). *BMC Med*. 2023;21(1):212.
130. Hsia DS, Lim M, Beyl RA, Hasan HA, Gardner J. 153-LB: initial presentation of children with type 2 diabetes during the COVID-19 pandemic. *Diabetes*. 2021;70(Suppl 1):153-LB.
131. Jabbour S, Seufert J, Scheen A, Bailey CJ, Karup C, Langkilde AM. Dapagliflozin in patients with type 2 diabetes mellitus: a pooled analysis of safety data from phase IIb/III clinical trials. *Diabetes Obes Metab*. 2018;20(3):620-628.
132. Jang HY, Kim IW, Oh JM. Comparative safety analysis of empagliflozin in type 2 diabetes mellitus patients with chronic kidney disease versus Normal kidney function: a Nationwide cohort study in Korea. *Pharmaceutics*. 2023;15(10):2394. doi:10.3390/pharmaceutics15102394
133. Kim GL, Chun S, Yu J. Thyroid dysfunction and autoimmune thyroiditis in children with new-onset diabetes mellitus. *Horm Res Paediatr*. 2021;94(Suppl 1):413.
134. Kim YG, Jeon JY, Han SJ, Kim DJ, Lee KW, Kim HJ. Sodium-glucose co-transporter-2 inhibitors and the risk of ketoacidosis in patients with type 2 diabetes mellitus: a nationwide population-based cohort study. *Diabetes Obes Metab*. 2018;20(8):1852-1858.
135. Kiss Z, Rokszin G, Abonyi-Toth Z, et al. Young adult patients with type 1 diabetes have a higher risk of mortality than those of similar age with type 2 diabetes: a nationwide analysis in Hungary. *Diabetes Metab Res Rev*. 2019;35(8):e3190.
136. Klingensmith GJ, Connor CG, Ruedy KJ, et al. Presentation of youth with type 2 diabetes in the pediatric diabetes consortium. *Pediatr Diabetes*. 2016;17(4):266-273.
137. Kohler S, Zeller C, Iliev H, Kaspers S. Safety and tolerability of empagliflozin in patients with type 2 diabetes: pooled analysis of phase I-III clinical trials. *Adv Ther*. 2017;34(7):1707-1726.
138. Kovesdy C, Schmedt N, Folkerts K, et al. Predictors of cardio-kidney complications and treatment failure in patients with chronic kidney disease and type 2 diabetes treated with SGLT2 inhibitors. *BMC Med*. 2022;20(1):2.
139. Kruljac I, Cacic M, Cacic P, et al. Diabetic ketosis during hyperglycemic crisis is associated with decreased all-cause mortality in patients with type 2 diabetes mellitus. *Endocrine*. 2017;55(1):139-143.
140. Kubota-Mishra EA, Huang XC, Minard CG, et al. 1250-P: identifying pediatric A-ß+ ketosis-prone diabetes (KPD). *Diabetes*. 2022;71-(Suppl 1):1250-P.
141. Lok CW, Wong MC, Yip KW, Ching WK, Choi EKY. Validation of the traditional Chinese version of the diabetes eating problem survey-

revised and study of the prevalence of disordered eating patterns in Chinese patients with type 1 DM. *BMC Psychiatry*. 2023;23(1):382.
142. Lund S, Solimando F, Kohler S, Zeller C, Kaspers S. Effect of empagliflozin on diabetic ketoacidosis in patients with type 2 diabetes: pooled clinical trial data. *Diabetologie Und Stoffwechsel*. 2017;12-(Suppl 1):S1-S84.
143. McCoy RG, Galindo RJ, Swarna KS, et al. Sociodemographic, clinical, and treatment-related factors associated with hyperglycemic crises among adults with type 1 or type 2 diabetes in the US from 2014 to 2020. *JAMA Netw Open*. 2021;4(9):e2123471.
144. McGurnaghan SJ, Brierley L, Caparrotta TM, et al. The effect of dapagliflozin on glycaemic control and other cardiovascular disease risk factors in type 2 diabetes mellitus: a real-world observational study. *Diabetologia*. 2019;62(4):621-632.
145. McSweeney Z, Fernandez E, Simpson J, McSweeney M, Hart-Unger S. Increased incidence of pediatric type 2 diabetes diagnoses during the COVID-19 pandemic. *Horm Res Paediatr*. 2022;95(Suppl 1):90-91.
146. Mendelsohn AB, Nam YH, Marshall J, McDermott C, Toh S, Lockhart C. Utilization, user characteristics, and adverse outcomes of insulin glargine originators and follow-on drug in patients with diabetes in the US. *Pharmacoepidemiol Drug Saf*. 2022;31(S2):523.
147. Mkparu N, Costacou T, Barinas-Mitchell E, Libman I. 1034-P: No "honeymoon" for youth, in particular blacks, diagnosed with diabetes during the first year of the COVID-pandemic. *Diabetes*. 2022;71-(Suppl 1):1034-P.
148. Monteiro P, Bergenstal RM, Toural E, et al. Efficacy and safety of empagliflozin in older patients in the EMPA-REG OUTCOME(R) trial. *Age Ageing*. 2019;48(6):859-866.
149. Moreno DM, Ramos RJA, Fernández LG, et al. Clinical/biochemical characteristics and related outcomes in people with new-onset diabetes and COVID-19: experience from a single centre. *Prac Diabetes*. 2022;39(6):24-31.
150. Nip A, Ahmad T. 183-LB: incidence and characteristics of type 1 and type 2 diabetes among youths in the COVID-19 pandemic. *Diabetes*. 2021;70(Suppl 1):183-LB.
151. Nip ASY, Reboussin BA, Dabelea D, et al. Disordered eating behaviors in youth and young adults with type 1 or type 2 diabetes receiving insulin therapy: the SEARCH for diabetes in youth study. *Diabetes Care*. 2019;42(5):859-866.
152. Oytun MG, Ceylan S, Koca M, et al. Benefits vs risks: SGLT-2 inhibitors in older adults living with frailty: a retrospective study from a university hospital. *Int J Diabetes Dev Countr*. 2023;43(5):758-764.
153. Patil T, Cook M, Hobson J, Kaur A, Lee A. Evaluating the safety of sodium-glucose Cotransporter-2 inhibitors in a Nationwide veterans health administration observational cohort study. *Am J Cardiol*. 2023;201:281-293.
154. Patorno E, Pawar A, Bessette LG, et al. Comparative effectiveness and safety of sodium-glucose cotransporter 2 inhibitors versus glucagon-like peptide 1 receptor agonists in older adults. *Diabetes Care*. 2021;44(3):826-835.
155. Patorno E, Pawar A, Franklin JM, et al. Empagliflozin selected cardiovascular and safety outcomes in routine care: first results from the EMPagliflozin compaRative effectIveness and SafEty (EMPRISE) study. *Diabetologia*. 2019;62(Suppl 1):55.
156. Patorno E, Pawar A, Wexler DJ, et al. Effectiveness and safety of empagliflozin in routine care patients: results from the EMPagliflozin compaRative effectIveness and SafEty (EMPRISE) study. *Diabetes Obes Metab*. 2022;24(3):442-454.
157. Patorno E, Tesfaye H, Wexler DJ, et al. 792-P: comparative safety of empagliflozin in routine care patients: interim results from the empagliflozin comparative effectiveness and safety (EMPRISE) study. *Diabetes*. 2021;70(Suppl 1): 792-P.
158. Patty YFPP, Y N, Libriansyah. Cost of illness analysis of diabetes mellitus with complications in one hospital in Surabaya. *Pharm Educ*. 2022;22(2):254-258.
159. Polcwiartek C, Kragholm K, Rohde C, Hashemi N, Vang T, Nielsen J. Diabetic ketoacidosis and diabetes associated with antipsychotic exposure among a previously diabetes-naive population with schizophrenia: a nationwide nested case-control study. *Diabetologia*. 2017;60(9):1678-1690.
160. Preechasuk L, Tantasuwan S, Likitmaskul S, et al. Clinical characteristics, glycemic control, and microvascular complications compared between young-onset type 1 and type 2 diabetes patients at Siriraj hospital - a tertiary referral center. *Diabetes Metab Syndr Obes*. 2022;15:1375-1387.
161. Qiu R, Balis D, Xie J, Davies MJ, Desai M, Meininger G. Longer-term safety and tolerability of canagliflozin in patients with type 2 diabetes: a pooled analysis. *Curr Med Res Opin*. 2017;33(3):553-562.
162. Riveline JP, Roussel R, Vicaut E, et al. Reduced rate of acute diabetes events with flash glucose monitoring is sustained for 2 years after initiation: extended outcomes from the RELIEF study. *Diabetes Technol Ther*. 2022;24(9):611-618.
163. Rodriguez G, Cabesaz F, Li J, et al. Clinical characteristics and outcomes among COVID 19 hospitalized patients in a Community Hospital in new York City. *J Endocrinol Soc*. 2021;5(Suppl 1):A336-A337.
164. Sarigumba M, Aragon J, Kanapi MP. Baseline glycemic status and outcome of persons with type 2 diabetes with COVID-19 infections: a single-center retrospective study. *J ASEAN Fed Endocr Soc*. 2021;36(1):45-49.
165. Song C, Brown A, Winstead R, et al. One year outcome of SGLT2 inhibitors amongst diabetic kidney transplant recipients. *J Am Soc Nephrol*. 2022;33:546.
166. Tallon E, Ebekozien O, Sanchez J, et al. Factors associated with hospitalization in youths and young adults with type 2 diabetes and COVID-19 infection. *Pediatr Diabetes*. 2021;22(Suppl 30):34.
167. Trepatchayakorn S, Supornsilchai V, Wacharasindhu S, Aroonparkmongkol S, Sahakitrungruang T. Trends and characteristics of childhood diabetes in a tertiary care center in Thailand. *Asian Biomed*. 2014;8(6):707-715.
168. Van Name MA, Cheng P, Gal RL, et al. Children and adolescents with type 1 and type 2 diabetes mellitus in the pediatric diabetes consortium registries: comparing clinical characteristics and glycaemic control. *Diabet Med*. 2020;37(5):863-867.
169. Wen X, Zeng N, Zhang N, et al. Diabetes complications and related comorbidities impair the accuracy of FreeStyle libre, a flash continuous glucose monitoring system, in patients with type 2 diabetes. *Diabetes Metab Syndr Obes*. 2022;15:3437-3445.
170. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2019;380(4):347-357.
171. Yabe D, Yasui A, Ji L, et al. Safety and tolerability of empagliflozin in east Asian patients with type 2 diabetes: pooled analysis of phase I-III clinical trials. *J Diabetes Invest*. 2019;10(2):418-428.
172. Yeaw J, Halinan S, Hines D, et al. Direct medical costs for complications among children and adults with diabetes in the US commercial payer setting. *Appl Health Econ Health Policy*. 2014;12(2):219-230.
173. Zaman Huri H, Permalu V, Vethakkan SR. Sliding-scale versus basal-bolus insulin in the management of severe or acute hyperglycemia in type 2 diabetes patients: a retrospective study. *PLoS One*. 2014;9(9):e106505.
174. Zelniker TA, Raz I, Mosenzon O, et al. Effect of dapagliflozin on cardiovascular outcomes according to baseline kidney function and albuminuria status in patients with type 2 diabetes: a prespecified secondary analysis of a randomized clinical trial. *JAMA Cardiol*. 2021;6(7):801-810.
175. Zhong VW, Juhaeri J, Mayer-Davis EJ. Trends in hospital admission for diabetic ketoacidosis in adults with type 1 and type 2 diabetes in England, 1998-2013: a retrospective cohort study. *Diabetes Care*. 2018;41(9):1870-1877.
176. Zhou XY, Huang SF, Lin JX, et al. Clinical characteristics and acute complication of COVID-19 patients with diabetes: a multicenter,

retrospective study in southern China. *Front Endocrinol (Lausanne)*. 2023;14:1237832.
177. Abrahami D, D'Andrea E, Kim SC, Wexler DJ, Paik JM, Patorno E. 1145-P: individual SGLT2 inhibitors and the risk of diabetic ketoacidosis. *Diabetes*. 2022;71(Suppl 1):1145-P.
178. Dawwas D, Leonard CE, Lewis JD. Risk of diabetic ketoacidosis with sodium-glucose transporter-2 inhibitors compared to dipeptidyl peptidase-4 (DPP4) inhibitors and sulfonylureas in patients with type 2 diabetes. *Pharmacoepidemiol Drug Saf*. 2021;30(Suppl 1): 54-55.
179. Ebrahimi F, Kutz A, Christ ER, Szinnai G. Lifetime risk and healthcare burden of diabetic ketoacidosis: a population-based study. *Front Endocrinol Lausanne*. 2022;13:940990.
180. Edmonston D, Mulder H, Lydon E, et al. Comparative kidney and cardiovascular effectiveness of empagliflozin compared to dipeptidyl Peptidase-4 inhibitors in patients with type 2 diabetes mellitus. *J Am Soc Nephrol*. 2023;34:856-857.
181. Karasik A, Lanzinger S, Chia-Hui Tan E, et al. Empagliflozin cardiovascular and renal effectiveness and safety compared to dipeptidyl peptidase-4 inhibitors across 11 countries in Europe and Asia: results from the EMPagliflozin compaRative effectIveness and SafEty (EMPRISE) study. *Diabetes Metab*. 2023;49(2):101418.
182. Sato Y, Morita K, Okada A, Matsui H, Fushimi K, Yasunaga H. Factors affecting in-hospital mortality of diabetic ketoacidosis patients: a retrospective cohort study. *Diabetes Res Clin Pract*. 2021;171: 108588.
183. Kaewput W, Thongprayoon C, Varothai N, et al. Prevalence and associated factors of hospitalization for dysglycemia among elderly type 2 diabetes patients: a nationwide study. *World J Diabetes*. 2019;10(3):212-223.
184. McGurnaghan SJ, Weir A, Bishop J, et al. Risks of and risk factors for COVID-19 disease in people with diabetes: a cohort study of the total population of Scotland. *Lancet Diabetes Endocrinol*. 2021;9(2): 82-93.
185. Caparrotta TM, Blackbourn LAK, Colhoun HM, McKeigue PM, McGurnaghan SJ. Investigating effectiveness and safety of sodium-glucose co-transporter 2 inhibitors in type 2 diabetes in Scotland: a real-world observational pharmacoepidemiology study. *Diabet Med*. 2023;40(S1):86.
186. Fu E, D'Andrea E, Wexler DJ, Patorno E, Paik JM. Safety of sodium-glucose Cotransporter-2 inhibitors in patients with CKD and type 2 diabetes. *J Am Soc Nephrol*. 2022;33:673.
187. Nikhil B, Himanshu G, Gaurav S, Anshaj M. Macrovascular and microvascular complications in newly diagnosed type 2 diabetes mellitus. *Indian J Public Health Res Dev*. 2022;13(3):199-204.
188. Clark A, Kraut E, Yen HH, Moore S, Hopman W, Houlden RL. Evaluation of a diabetic ketoacidosis order set in adults with type 1 and type 2 diabetes at a tertiary academic medical Centre: a retrospective chart audit. *Can J Diabetes*. 2019;43(5):304-308.e3.
189. Gnaneshwari SJ, Kavyashree SM, Mohapatra S, Banu R. Clinical profile, precipitating events and metabolic abnormalities in patients with diabetic ketoacidosis. *J Cardiovasc Dis Res*. 2023;14(6):2168-2175.
190. Gorchane A, Ach T, Sahli J, et al. Uncovering the alarming rise of diabetic ketoacidosis during COVID-19 pandemic: a pioneer African study and review of literature. *Front Endocrinol (Lausanne)*. 2023;14: 1234256.
191. Kolesnyk A, Rengarajan L, Wallett L, et al. Differences in presentation, management and complications of diabetic ketoacidosis in type 1 and type 2 diabetes. *Diabet Med*. 2021;38(S1):1.
192. Ndebele NFM, Naidoo M. The management of diabetic ketoacidosis at a rural regional hospital in KwaZulu-Natal. *Afr J Prim Health Care Fam Med*. 2018;10(1):e1-e6.
193. Rengarajan L, Ooi E, Melson E, et al. How common is diabetic ketoacidosis (DKA) in persons with type 2 diabetes? Retrospective review of aetiology and outcome of 307 consecutive DKA episodes from a tertiary centre. *Br J Diabetes*. 2021;21(1):6.
194. Tiwari RK, Gokhroo A, Phepale K, Jain R, Kumar VP. Dynamic changes in serum phosphorus level during treatment of diabetic ketoacidosis and predicted by degree of metabolic acidosis on presentation. *J Indian Acad Clin Med*. 2017;18(1):26-28.
195. Misra S, Barron E, Vamos E, et al. Temporal trends in emergency admissions for diabetic ketoacidosis in people with diabetes in England before and during the COVID-19 pandemic: a population-based study. *Lancet Diabetes Endocrinol*. 2021;9(10):671-680.
196. Shaka H, Wani F, El-Amir Z, et al. Comparing patient characteristics and outcomes in type 1 versus type 2 diabetes with diabetic ketoacidosis: a review and a propensity-matched nationwide analysis. *J Invest Med*. 2021;69(6):1196-1200.
197. Frank JR, Blissett D, Hellmund R, Virdi N. Budget impact of the flash continuous glucose monitoring system in Medicaid diabetes beneficiaries treated with intensive insulin therapy. *Diabetes Technol Ther*. 2021;23(S3):S36-S44.
198. Guisado-Vasco P, Cano-Megias M, Carrasco-de la Fuente M, Corres-Gonzalez J, Matei AM, Gonzalez-Albarran O. Clinical features, mortality, hospital admission, and length of stay of a cohort of adult patients with diabetic ketoacidosis attending the emergency room of a tertiary hospital in Spain. *Endocrinol Nutr*. 2015;62(6): 277-284.
199. Hao S, Cossen K, Vellanki P. SARS-CoV-2 does not increase severity of diabetic ketoacidosis in children and adolescents with new onset ketosis prone diabetes. *Am J Med Sci*. 2023;365(Suppl 1):S68.
200. ElSayed NA, Aleppo G, Aroda VR, et al. 2. Classification and diagnosis of diabetes: standards of Care in Diabetes-2023. *Diabetes Care*. 2023;46(Suppl 1):S19-S40.
201. Li CX, Liu TT, Zhang Q, et al. Safety of sodium-glucose transporter 2 (SGLT-2) inhibitors in patients with type 2 diabetes: a meta-analysis of cohort studies. *Front Pharmacol*. 2023;14:1275060.
202. Al-Hindi B, Mohammed MA, Mangantig E, Martini ND. Prevalence of sodium-glucose transporter 2 inhibitor-associated diabetic ketoacidosis in real-world data: a systematic review and meta-analysis. *J Am Pharm Assoc*. 2024;64(1):9-26.e26.
203. Scheen AJ. Pharmacodynamics, efficacy and safety of sodium-glucose co-transporter type 2 (SGLT2) inhibitors for the treatment of type 2 diabetes mellitus. *Drugs*. 2015;75(1):33-59.
204. Perry RJ, Shulman GI. Sodium-glucose cotransporter-2 inhibitors: understanding the mechanisms for therapeutic promise and persisting risks. *J Biol Chem*. 2020;295(42):14379-14390.
205. Wallenius K, Kroon T, Hagstedt T, et al. The SGLT2 inhibitor dapagliflozin promotes systemic FFA mobilization, enhances hepatic beta-oxidation, and induces ketosis. *J Lipid Res*. 2022; 63(3):100176.
206. American Diabetes Association Professional Practice Committee. 10. Cardiovascular disease and risk management: standards of Care in Diabetes-2024. *Diabetes Care*. 2024;47(Suppl 1):S179-S218.
207. American Diabetes Association Professional Practice Committee. 9. Pharmacologic approaches to glycemic treatment: standards of Care in Diabetes-2024. *Diabetes Care*. 2024;47(Suppl 1):S158-S178.
208. Kovacs A, Bunduc S, Veres DS, et al. One third of cases of new-onset diabetic ketosis in adults are associated with ketosis-prone type 2 diabetes-a systematic review and meta-analysis. *Diabetes Metab Res Rev*. 2024;40(3):e3743.
209. Barkai LJ, Gombos T, Lukacs K, et al. Ketosis-prone type 2 diabetes among newly diagnosed adult Caucasian patients: a follow-up study. *Diabetes*. 2016;65(Suppl 1):A597.

210. American Diabetes Association Professional Practice Committee. 7. Diabetes technology: standards of Care in Diabetes-2024. *Diabetes Care*. 2024;47(Suppl 1):S126-S144.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Wysham C, Bindal A, Levrat-Guillen F, Kostadinova D, Poon Y. A systematic literature review on the burden of diabetic ketoacidosis in type 2 diabetes mellitus. *Diabetes Obes Metab*. 2025;27(5):2750-2767. doi:10.1111/dom.16282