Association between SGLT2 inhibitor treatment and diabetic ketoacidosis and mortality in people with type 2 diabetes admitted to hospital with COVID-19

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Abstract

Objective

To determine the association between prescription of SGLT2 inhibitors and diabetic ketoacidosis (DKA) incidence or mortality in people with type 2 diabetes hospitalized with COVID-19.

Research Design and Methods

This was a retrospective cohort study based on secondary analysis of data from a large nationwide audit from a network of 40 centres in United Kingdom with data collection up to December 2020 that was originally designed to describe risk factors associated with adverse outcomes among people with diabetes who were admitted to hospital with COVID-19.. The primary outcome for this analysis was DKA on or during hospital admission. The secondary outcome was mortality. Crude, age-sex adjusted and multivariable logistic regression models, were used to generate odds ratios and 95% confidence intervals for people prescribed SGLT2 inhibitor compared to those not prescribed SGLT2 inhibitor.

Results

The original national audit included 3067 people with type 2 diabetes who were admitted to hospital with COVID-19, of whom 230 (7.5%) were prescribed SGLT2 inhibitors prior to hospital admission. Mean (SD) age of the overall cohort was 72 years, 62.3% were men and 34.9% were prescribed insulin. Overall, 2.8% of the total population had DKA and 35.6% people died. The adjusted odds of DKA were not significantly different between those prescribed SGLT2 inhibitors and those not (OR 0.56, 0.16-1.97). The adjusted odds of mortality associated with SGLT2 inhibitors were similar in the total study population (OR 1.13, 0.78-1.63), in the sub-group prescribed insulin (OR 1.02, 0.59-1.77), and in the sub-group that developed DKA (OR 0.21, 0.01-8.76).

Conclusions

We demonstrate a low risk of DKA and high mortality rate in people with type 2 diabetes admitted to hospital with COVID-19 and limited power but no evidence of increased risk of DKA or in-hospital mortality associated with prescription of SGLT2 inhibitors.

Background

Increasing age, socio-economic deprivation, male sex, chronic diseases including diabetes, and non-white ethnicity have been associated with worse outcomes from Coronavirus disease 2019 (COVID-19). (1)The risk of hospital-related COVID-19 mortality is increased three-fold with type 1 diabetes and two-fold with type 2 diabetes. (2)Diabetic ketoacidosis (DKA) has been reported with COVID-19 and is associated with a 50 % increased risk of mortality.(3) DKA is a recognised life-threatening consequence of COVID-19 in those with type 1 diabetes. It is most frequently encountered in people with type 1 diabetes but can also occur in people with type 2 diabetes, typically during an acute illness, such as sepsis, myocardial infarction or stroke, surgery and other stressors, glucocorticoids, alcohol consumption, or reductions in calorie intake.(4)

Sodium glucose co-transporter 2 (SGLT2) inhibitors have been shown to reduce risk of cardiovascular and kidney events in large randomised trials of people with type 2 diabetes.(5) However, the US Food and Drug Administration (FDA) published a safety update in 2015 about the association between SGLT2 inhibitor use and risk of DKA.(6) During the pandemic, a greater proportion of people presenting with DKA have had type 2 diabetes than previously.(7) Recent consensus statements have recommended that SGLT2 inhibitors are safe for use in routine clinical care during the COVID-19 pandemic but that SGLT2 inhibitors should be stopped in symptomatic individuals infected with SARS-CoV-2, who might be at risk of euglycaemic DKA particularly if admitted to hospital.(8)

A number of observational studies have have reported that the use of SGLT2 inhibitor therapies are not associated with worse outcomes in people with COVID-19.(9, 10) A recent population-based study in England of nearly 3 million people reported an 18% lower risk of COVID-19-related mortality in people with type 2 diabetes prescribed SGLT2 inhibitors, compared to people prescribed other glucose lowering therapies, although the authors concluded that their findings were likely to be confounded by indication for SGLT2 prescribing.(11) In addition, the recent results from the Dapagliflozin in Respiratory failure in patients with COVID-19 (DARE-19) randomised controlled

trial of dapagliflozin, an SGLT2 inhibitor, among people with at least one cardiometabolic risk factor (i.e., hypertension, type 2 diabetes (present in 51% of the population), atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease) demonstrated that the incidence of DKA in severely unwell patients admitted with COVID-19 was very low, with only 2 cases from a total of 312 participants with history of type 2 diabetes randomised to dapagliflozin.(12) These cases were identified through protocol-mandated laboratory monitoring and both events resolved rapidly and completely. There were also no other safety signals and no statistically significant association between dapaglifozin and mortality (HR 0.77 95% CI 0.53-1.16 for the whole population). However, the incidence of DKA and mortality in people with type 2 diabetes who were prescribed an SGLT2 inhibitor prior to hospital admission with COVID-19 has not been well documented. The aim of this study was secondary analysis of data from a large, robust national audit to determine the association between prior prescription of SGLT2 inhibitors and DKA incidence or mortality in people with type 2 diabetes hospitalised with COVID-19.

Methods

Data were collected through a nationwide audit from a network of 40 centres in United Kingdom conducted by the Association of British Clinical Diabetologists (ABCD).(13) The ABCD has a long-established infrastructure for nationwide audits to allow diabetes specialist teams across the UK to collect real-world data on specific therapies and technologies.(13) The COVID-19 and diabetes nationwide audit commenced in September 2020 and data were collected up to 8th December 2020. Centres were asked to collate data from patient records from the start of the pandemic in March 2020 and to transfer the anonymized data to the National Institute for Health Research (NIHR) Health Informatics Collaborative (HIC) Coordinating Centre within the Oxford University Hospitals National Health Service (NHS) Foundation Trust. Diabetes specialist team members at each participating hospital identified patients with diabetes admitted with COVID-19 and positive SARS-CoV-2 test. An audit data collection form was provided to each participating centre, where pseudonymized data were held on secure servers.

Data were transferred securely using the National Health Service (NHS) network. Submissions were checked by the NIHR HIC team and additional information was sought from contributing centres where necessary to ensure completeness and accuracy. The cleaned data was locked on MS SQL server and made available for analysis by a Labkey portal. The data were processed and analyzed on a secure server at Oxford University Hospital. Cases of DKA were identified by diabetes specialists at each centre. The primary analysis included every case of contributor-identified DKA, whether occurring on admission to hospital, or subsequently during inpatient treatment. Adjudication of DKA cases by two experienced clinicians (figure 1) and a sensitivity analysis were also performed, including only those cases in which biochemistry results on admission to hospital met the diagnostic criteria of the Joint British Diabetes Societies Inpatient Group (JBDS-IP) guideline on diagnosis and management of DKA.(14)

Ethical approval

The audit was registered with the OUH and a Data Protection Impact Assessment was carried out and approved by the OUH Caldicott Guardian and the Public Benefit and Privacy Panel in Scotland (reference 2021-0111) and there was no requirement for approval by a research ethics committee. ABCD audits have a long track record of supporting clinical practice in the NHS, which itself supports such work with clear guidance for contributing centres on the secure use of routine healthcare data. The ABCD audit remains open and the original data collection sheet can be obtained from the ABCD secretariat.

Study variables

We collected demographic and clinical data. Demographic data included age in years at hospital admission, sex, ethnicity, and Index of Multiple Deprivation decile, an area-based measure of socio-economic status derived using the postcode (zip code equivalent) for place of residence. Clinical characteristics included weight and height, or BMI; smoking status, type and duration of diabetes, diabetes complications including diabetic foot ulcer, diabetic nephropathy, diabetic peripheral neuropathy, diabetic retinopathy, peripheral vascular disease, ischemic heart disease (myocardial

infarction and/or heart failure), cerebrovascular disease (stroke/transient ischemic attack), and other significant comorbidities including hypertension, dementia, asthma, chronic obstructive pulmonary disease and malignant neoplasm. Medication history included antidiabetic medications and other prespecified therapy classes (angiotensin converting enzyme inhibitor or angiotensin receptor antagonist, oral corticosteroid, statin, antiplatelet, anticoagulant, and regular nonsteroidal anti-inflammatory drug). Laboratory data included latest pre-admission HbA_{1c} and serum creatinine, and admission blood glucose, pH, bicarbonate, lactate, serum creatinine and capillary blood ketones. Dates of the start and finish (if applicable) of each hospital admission were collected, along with the date of positive SARS-CoV-2 test which was a prerequisite for inclusion in the study. Recorded outcomes included vital status and admission to an intensive care unit (ICU). For this analysis, we only included people in the audit with T2DM.

Statistical analysis

Baseline clinical characteristics are reported as frequency and percentages for categorical variables, and as mean and standard deviation for continuous variables by exposure status, defined as record or absence of record of SGLT2 inhibitor use prior to hospital admission. The primary outcome of the study was DKA. The secondary outcomes were mortality in the whole cohort, mortality in those with/without insulin administration and in those with DKA. Crude, age-sex adjusted and multivariable logistic regression models, were used to generate odds ratios and 95% confidence intervals. For the logistic regression analysis, continuous variables, including age and admission blood glucose, were used to generate odds ratios. Binary categorical variables were created to define sex, ethnicity (white or not), micro/macrovascular complications, DKA status, mortality, SGLT2 inhibitor prescription and insulin prescription. Sample size calculations were not performed as this was an exploratory analysis. All statistical analysis was performed using R version 3.3. P-values of less than 0.05 were considered statistically significant.

Results

The audit included 3067 people with type 2 diabetes who were admitted to hospital with COVID-19 and who had complete data, of whom 230 (7.5%) were prescribed SGLT2 inhibitors (Table 1). Mean age of the cohort was 72 years. 62.3% were men and 34.9% (994/2845) were prescribed insulin. SGLT2 inhibitors were more likely to be prescribed to males (73%) than females (61%), to patients who were on insulin (49% vs 34% not on insulin), people with diabetic foot ulcers (20% vs 7%), those with diabetic nephropathy (40% vs 23%), with peripheral vascular disease (28% vs 11%), with retinopathy (40% vs 23%) and to those with cardiovascular disease (47% vs 36%). Overall, 86/3067 (2.8%) had DKA and 1082/3039 (35.6%) people died. Table 2 shows the odds ratios (with 95% confidence intervals) for DKA and for death before and after adjusting for age, sex, ethnicity, admission blood glucose, insulin administration and micro/macrovascular disease, in people prescribed SGLT2 inhibitors compared to those not prescribed SGLT2 inhibitors. The odds of DKA did not differ significantly different between those prescribed SGLT2 inhibitors and those not (adjusted OR 0.56 (0.16-1.97). The odds of mortality associated with SGLT2 inhibitors were similar in the total study population (OR 1.13, 0.78-1.63), in the sub-group prescribed insulin (OR 1.02, 0.59 – 1.77) and in the sub-group that developed DKA (OR 0.21, 0.01 – 8.76). In a sensitivity analysis including only those cases in which admission biochemistry met the JBDS-IP diagnostic criteria for DKA,(14) the adjusted odds ratio for adjudicated DKA associated with a prescription of SGLT2 inhibitors and those not was 1.58 (0.35-7.08).

Discussion

To the best of our knowledge, this is the largest multicentre study reporting data on DKA and mortality in people with type 2 diabetes admitted to hospital with COVID-19 that investigates association with SGLT2 inhibitors pre-admission and suggests that that, despite limited power, there is no evidence for an association. Only a few small studies or case studies have recently reported high rates of DKA in people hospitalised with COVID-19, particularly in those with type 2 diabetes. (15)

Inpatient admission has been reported as a risk for SGLT2 inhibitor-associated DKA. In a retrospective multicentre cohort study from Australia, the risk of DKA in patients with type 2 diabetes

during inpatient admission was small but higher in SGLT2 inhibitor vs non-SGLT2 inhibitor users, with planned fasting and surgery being identified as potential risk factors.(16) There has also been a concern that routine SGLT2 inhibitor treatment could increase COVID-19-related risks through increased kidney expression of angiotensin-converting enzyme 2 (ACE2). One large retrospective nationwide database study of nearly 3 million people with type 2 diabetes in England recently reported that the adjusted hazard ratio for COVID-19-related mortality for people on SGLT2 inhibitors was 0.82 (95% CI, 0.74-0.91) compared to the group not prescribed any glucose-lowering therapies.(11) The study did not report DKA outcomes and concluded that overall differences in outcomes for all glucose-lowering therapies, including SGLT2 inhibitors, were small and likely to be confounded by indication. (11)

In the DARE-19 trial in which approximately 51% of participants had diabetes, dapagliflozin was well tolerated and overall there were fewer serious adverse events in those prescribed dapagliflozin compared to placebo. The DARE-19 trial recruited 312 participants who were randomised to dapagliflozin, while the current study included 230 patients who were on an SGLT2 inhibitor at hospital admission. Our cohort was older (mean age 69 years vs 61 year in the DARE-19 trial), with greater proportion of non-White ethnicity (31% vs 26% in DARE-19 trial), a similar BMI (31 kg/m^2), but higher prevalence of cardiovascular disease (47% vs 17%) and of nephropathy (33% vs 17% CKD in DARE-19 trial). Overall 10.6% in the dapagliflozin arm, and 13.3% in the placebo arm were reported to have serious adverse events. Safety events of acute kidney injury were reported in 3.4% patients in the dapagliflozin group and 5.5% in the placebo group. Participants in the DARE-19 trial were closely monitored for adverse events while patients in our study would have had routine hospital monitoring as per local protocols. Despite the cohort of patients in our study being at higher risk compared to the participants in the DARE-19 trial, we did not observe a significant increase in incidence of DKA in our study. In view of the DARE-19 trial results suggesting dapagliflozin may reduce organ failure and death among high risk individuals, investigators in the United Kingdom recently announced an empagliflozin treatment arm in the RECOVERY platform trial(17), and the National Institutes of Health (NIH) have added SGLT2 inhibitors to the Activ4a pragmatic trial

platform, which is evaluating promising treatments in patients hospitalized with COVID-19. Subsequently the Empagliflozin in patients hospitalised for Acute Heart Failure (EMPULSE) double-blind trial was published, in which 530 patients with acute de novo or decompensated chronic heart failure, of whom just under half had diabetes, were randomly assigned to empagliflozin 10 mg daily or placebo. (18)Initiation of empagliflozin resulted in a statistically significant and clinically meaningful benefit at 90 days with reductions in all deaths, hospitalisation for heart failure and improvements in quality of life (stratified win ratio 1.36, 95% CI 1.09-1.68) and no cases of DKA in the empagliflozin arm.

A smaller proportion of people (7.5%) included in our audit were prescribed SGLT2 inhibitors compared to 9.3% of people with type 2 diabetes prescribed them in the community. (11)Only 47% of people with cardiovascular disease and 40% with diabetic nephropathy were prescribed SGLT2 inhibitors despite international guideline recommendations for prescribing these novel therapies in high risk populations.(19) Interestingly, despite concerns about SGLT2 inhibitors increasing risk of diabetic foot ulceration, 26% of people in our study with foot ulcers were prescribed them. (19)

As well as the beneficial effects of SGLT2 inhibitors in patients admitted to hospital, another key concern is the potential for these cardiovascular and kidney protective therapies not being initiated following discharge from hospital. One US study of patients with type 2 diabetes hospitalized following a myocardial infarction showed that around half the patients following discharge from hospital may not have had their glucose-lowering therapy commenced post-discharge. (20)

There are several strengths to our study, besides being the largest multicentre study to report the association between history of SGLT2i prior to hospital admission with COVID-19 and DKA or mortality among people with type 2 diabetes. Data from the centres were collected using a structured proforma with admission variables defined specifically for this national COVID-19 audit. Each case of DKA was reviewed by senior clinicians using established criteria. (14)Limitations of the study include the opportunistic retrospective analysis of data collected in a rigorously conducted audit with

limited power rather than an adequately powered primary study. The data also relate only to patients admitted to hospital, excluding those not reaching, or not requiring, hospital treatment. Although we adjusted our analysis for several key risk factors there is potential for residual confounding. The admitted patients were a more sicker group as has been shown in previous studies and we therefore adjusted our analysis using a number of baseline variables associated with a higher risk of mortality.

We also had a number of patients with missing data for some variables. Another key limitation is that we do not know whether SGLT2 inhibitor treatment was stopped on admission, as recommended by national and international guidelines. Finally, while DKA incidence was ascertained by diabetes specialists in each contributing centre, adjudication of biochemical diagnosis was possible when DKA was present on admission, but not when it occurred after admission to hospital.

The safety of SGLT2i in people admitted with COVID-19 has not been well described during the COVID-19 pandemic. To our knowledge this is the largest multicentre study to report safety outcomes of DKA and death in people with T2DM admitted to hospital with COVID-19 with or without SGLT2 inhibitor treatment. We describe a low DKA risk and high in-hospital mortality in people with T2DM admitted to hospital with COVID-19 overall, but no evidence for an increase in risk of DKA or in-hospital mortality associated with prescription of SGLT2 inhibitors albeit on the basis of imprecise estimates. Furthermore, there were no evidence of safety concerns for those prescribed SGLT2 inhibitors in people with or without DKA in this population at very high risk of mortality. Previous recommendations to stop SGLT2 inhibitors during acute illness particularly admission even during COVID-19 have been based on consensus. In view of the results of the DARE-19 and EMPULSE trials and of our study, we believe that careful consideration should be given to the risks and benefits of continuing treatment in people admitted to hospital on SGLT2 inhibitors in view of their cardiovascular and kidney benefits. If SGLT2 inhibitors are continued than there should be careful monitoring for development of DKA. We recommend further adequately powered randomised controlled trials and observational studies to determine the safety of SGLT2 inhibitors in people acutely admitted to hospital.

Guarantor statement:

KK is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Author Contributions:

KK and YR co-designed the study analysis. KK and YR carried out the data analysis. KK and YR drafted the manuscript. All authors contributed to the interpretation of the results and critical review of the paper.

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Duality of Interest

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Table 1. Demographic and clinical characteristics of patients with type 2 diabetes and COVID-19 admitted to hospital during the first wave of COVID-19 in the UK who were included in the ABCD audit

Demographics and clinical characteristics	**Prescribed SGLT2i(N = 230)**	**Not on SGLT2i (N = 2837)**	**P-value**
Mean (SD) Age (years)	69(13)	73(14)	0.12
Men, %	167, 73%	1743, 61%	<0.01
White ethnicity (%)	146(69%)	1743(66%)	0.59
Mean (SD) BMI, kg/m2	30.4(7.3)	29.3(7.1)	0.31
Mean (SD) most recent HbA1c (mmol/mol)	67(22)	57(25)	<0.01
Mean (SD) admission blood glucose (mmol/l)	11.3(7.1)	10.9(6.4)	0.11
Mean (SD) serum creatinine (µmol/l)	134(134)	153(160)	<0.01
Prescribed inulin (%)	104/213(49%)	890/2632(34%)	<0.01
Diabetic foot ulcer (%)	49/185(26%)	157/2176(7%)	<0.01
Diabetic nephropathy (%)	64/194(33%)	536/2214(24%)	<0.01
Diabetic peripheral neuropathy (%)	137/203(67%)	194/2294(8%)	<0.01
Diabetic retinopathy (%)	68/171(40%)	500/2147(23%)	<0.01
Peripheral vascular disease (%)	50/181(28%)	252/2294(11%)	<0.01
Ischaemic heart disease and cerebrovascular disease (%)	89/190(47%)	744/2075(36%)	<0.01
Hypertension (%)	158/217(73%)	1866/2711(69%)	0.25
Dementia (%)	22/207(11%)	376/2529(15%)	0.12
Asthma (%)	26/209(12%)	362/2668(14%)	0.72
COPD (%)	27/207(13%)	362/2486(15%)	0.62
Malignant neoplasm (%)	30/212(14%)	412/2714(15%)	0.76

Table 2. Numbers and proportions of in-hospital deaths and people with DKA in people with type 2 diabetes admitted to hospital during the first wave of COVID-19 in people included in ABCD audit in the UK and odds ratios for the association between being prescribed SGLT2i and for the whole group and sub-groups of interest

OUTCOMES	**N**	**Prescribed SGLT2i**	**Not on SGLT2i**	**Univariate OR (95% CI)**	**Age and sex adjusted (OR odds ratio 95% CI)**	**Age, sex, ethnicity, admission blood glucose, insulin administration, micro/macrovascular disease* adjusted (OR odds ratio 95% CI)**
Primary Outcome						
Developed DKA	86/3067	7/230(3.0%)	79/2837(2.8%)	1.10(0.50-2.40)	0.96(0.43-2.11)	0.56(0.16-1.97)
Secondary Outcome						
Death (Whole cohort)	1082/3039	84/228(36.8%)	998/2811 (35.5%)	1.06(0.80-1.40)	1.25(0.93-1.67)	1.13(0.78-1.63)
Death in those not on insulin	695/1827	41/107(38.3%)	654/1720(38.0%)	1.01(0.68-1.51)	1.18(0.77-1.79)	1.13(0.66-1.93)
Death in those on insulin	359/924	38/104(36.2%)	321/886(36.2%)	1.01(0.66-1.55)	1.18(0.76-1.82)	1.02(0.59-1.77)
Death in those with DKA	29/86	2/7(28.6%)	27/79(34.2%)	0.77(0.14-4.24)	0.69 (0.11-4.50)	0.21(0.01-8.76)

* microvascular disease is defined as having at least one complication from diabetic nephropathy, diabetic peripheral neuropathy or diabetic retinopathy; macrovascular disease is defined as having at least one complication from peripheral vascular disease or ischaemic heart disease/cerebrobascular disease.

Figure 1: CONSORT diagram demonstrating (a) identification of the primary analysis cohort (Contributor-defined DKA), which comprises all instances of DKA that occurred during hospital stays with COVID-19 and diabetes, identified as such by the contributing clinicians, and (b) identification of the sensitivity analysis cohort (Adjudicated admission DKA), comprising all instances of DKA diagnosed at the time of hospital admission, for which the admission biochemistry results were adjudicated against Joint British Diabetes Societies Inpatient Care diagnostic criteria by two senior clinicians.