A series of diabetic ketoacidosis associated with the use of sodium-glucose co-transporter-2 inhibitors in secondary care

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Abstract

Background and aims

Sodium-glucose co-transporter-2 inhibitors (SGLT-2i) are associated with diabetic ketoacidosis (DKA), however limited case series are published.

Methods

We evaluated the characteristics of patients admitted with SGLT-2i associated DKA.

Results

Over 4 months, 22 patients were identified; 45.5% of DKA was not associated with concurrent illness.

Conclusion

DKA is not uncommonly associated with SGLT2i with no clear patient factors associated with severity.

Highlights

1. Sodium-glucose co-transporter-2 inhibitor (SGLT-2i) associated DKA was observed in 22 patients over 4-months.
2. No differences in age, diabetes duration, HbA1c or admission biochemistry were seen in those with concurrent illness.
3. Our results observed no clear association between patient characteristics or co-morbidity and SGLT-2i-associated DKA.

Introduction

Sodium glucose co-transporter 2 inhibitors (SGLT-2i) are associated with both euglycaemic ketoacidosis (EuDKA) and hyperglycaemic diabetic ketoacidosis (DKA). Other than individual case reports, there are few published case series of SGLT2i-associated DKA. Those available relate to EuDKA and have small numbers ranging from 2-5 cases.[1-4] The only retrospective prevalence study is a Canadian series which observed a prevalence of 6.6% amongst 647 hospital admissions with DKA over 4-years.[5] Anecdotally, we have noted an increase in the number of admissions of SGLT2i-associated DKA in the Autumn of 2021. Our aim was to descriptively examine the number and characteristics of patients admitted during a 4-month period. We are not aware of another series examining this prospectively in secondary care, therefore this work adds to the limited publications in this area.

Methods

Subjects

The work was undertaken as a routine evaluation of clinical practice. Patients were identified following referral to the diabetes team with SGLT2i-associated DKA between September-December 2021. Medical notes relating to the cases were examined and collected data verified by two or more authors (JS, ST, CE). Data were collected on a standardised proforma, including patient characteristics on admission, medication use, previous comorbidities and diagnoses.

The aim was to document the number of cases in a 4-month period along with the characteristics of the patient series.

Statistical Analysis

This was a descriptive case series. Discrete variables are described as number (%). Mean and standard deviation were used to describe the variables with a normal distribution; median and range were used when appropriate. Student's t-tests were used to compare continuous variables by DKA status and comorbidities on admission.

Results

Baseline Characteristics

During the 4-month period, 22 (13 males, 9 females) hospital patients were identified with DKA receiving concomitant SGLT2i therapy. The baseline characteristics of the patients are summarised in Table 1. The mean age was 60.8±12.3 years and mean pre-admission HbA1c 89.2±29.2 mmol/mol [10.3%]. All had a diagnosis of DKA based on admission glucose, blood ketone, plasma pH and bicarbonate. The majority of admissions (45.5%) had DKA alone, followed by concurrent infection or COVID-19 infection. We observed no significant differences in age, duration of diabetes, HbA1c, admission glucose, pH, and blood ketones between those with and without a concurrent illness. The mean serum lactate was 2.2±1.2 mmol/L [range 0.8-5.3 mmol/L], with 9 patients having a serum lactate >1.6mmol/L indicating a mixed acidosis. Of the 22 admissions, 19 (86.4%) were discharged alive, and 3 (13.6%) died during the admission (bacterial pneumonia, COVID-19 pneumonia, and myocardial infarction each associated with DKA).

Diabetes medication and co-morbidities on admission

There was considerable treatment heterogeneity on admission. As shown in Figure 1, in addition to an SGLT2i:- 9 patients received oral therapies; 5 patients received

insulin, and 4 received a combination of insulin with oral agents or a GLP-1 receptor analogue; 3 were taking one or more oral agents; and 1 treated with an SGLT2i alone. Oral therapies consisted of combinations of metformin, sulphonylurea and dipeptidyl peptidase-4 (DPP-4) inhibitors. For those receiving insulin the median (range) of the total daily dose was 50 (24-92) units (mean 53.8±24.9 units).

A previous history of comorbidities were not present in 13 (59.1%) patients. Two patients (9.1%) had respiratory disease. In addition, 1 patient (4.5%) had: cancer; coronary heart disease (CHD); respiratory disease with cancer; CHD with heart failure; heart failure with co-existing respiratory disease and CHD; CHD with heart failure and chronic kidney disease. We observed no significant differences in age, duration of diabetes, HbA1c, admission glucose, pH or blood ketones between those with and without pre-existing comorbidities.

Discussion

This case series aimed to descriptively examine the number and characteristics of patients admitted with SGLT2i-associated DKA over a 4-month period. Most of the 22 patients (45.5%) were admitted with DKA alone, 27.3% were admitted with DKA and infection and a further 18.2% with DKA and COVID-19. Indeed, a precipitating cause is not always identified in patients presenting in DKA on SGLT2i therapy.[1-4] Ata et al, found no precipitating cause for DKA in 55% of their patient group admitted with DKA on SGLT2i, and 32% were admitted with DKA and infection.[1] Contrariwise, Clark et al[5] suggested that SGLT2i use was the only precipitator for DKA in 11.6% of their patients and found infection precipitated DKA in 23.3%. Prolonged fasting has been suggested

as another precipitating cause for DKA in patients using SGLT2i,[6] however our study did not observe this finding.

In our series, COVID-19 infection was present in 18.4% of patients in DKA and has been observed in a few previously published case reports of COVID-19 precipitating EuDKA in patients using SGLT2i.[7-9] It is well-known that concurrent illness and metabolic stress can incite DKA in patients on SGLT2i, and diabetes mellitus is a well-established risk factor for severe COVID-19, whilst COVID-19 patients often present with severe hyperglycemia.[10] However, given the cardioprotective role of SGLT2i the exact interplay between COVID-19, DKA and SGLT2i remains unknown.

There is a two-fold greater risk of DKA associated with SGLT2i versus placebo or other glucose-lowering agents. This risk is higher in older patients with longer duration of type 2 diabetes (T2D) and reduced insulin-secreting capacity[9]. The mean age of patients in this study was 60.7±12.2 years, diabetes duration 15.6±8.8 years and HbA1c 89 mmol/mol [10.3%] indicating poorly-controlled diabetes. DKA may be explained by relative insulin deficiency and excess counter-regulatory hormone response (e.g. endogenous glucocorticoids, catecholamines, and glucagon) typical in physiological stress. In T2D of long duration or requiring insulin therapy, the risk of DKA is greater due to relative insulin deficiency. Of the 20 patients with T2D, 16 (75%) patients had a diagnosis for >12 years whilst the remaining 4 patients were aged 43-48 years and were subsequently managed as a diagnosis of latent autoimmune diabetes of adults (LADA) (GAD antibody positive in 3 cases).

As such the occurrence of DKA in this cohort can be explained by the relative insulin deficiency seen in those with long-standing and poorly-controlled T2D or who have been incorrectly diagnosed with T2D with underlying LADA. In such cases, SGLT-2 inhibition causes a paradoxical increase in endogenous glucose production, through enhanced gluconeogenesis.[11] This results from the reduced serum glucose levels induced by SGLT-2 inhibitor-mediated glycosuria enhancing gluconeogenesis by increasing the glucagon-insulin ratio by up to 25% in people with T2D. This shift stimulates hepatic gluconeogenesis, lipolysis and thereby ketogenesis, which in the context of poorly-controlled diabetes may precipitate DKA.[12] Of the 9 patients treated with insulin (2 patients with type 1 diabetes [T1D], 7 patients with T2D), limited data were available to determine whether patients missed insulin doses or whether there was inadequate dose escalation in keeping with sick-day rules.

There are no well-established patient characteristics which pre-dispose those taking SGLT2i to DKA or more severe ketoacidosis and this study corroborates this. Most patients had no prior comorbidity and there was no clear association between admission pH, glucose or ketones and comorbidity. However, statistical analyses are limited in this small cohort and therefore larger studies are needed to better establish any association between patient characteristics, SGLT2i and DKA.

It is interesting to note that only 1 patient (4.5%) in this cohort was admitted with EuDKA, and the remainder in hyperglycaemic DKA. This may be due to our cohort of patients with long-standing and poorly-controlled diabetes, possibly chance associated with the sample size or simply a consequence of under-recognition in hospitalised patients. Raising awareness of EuDKA is essential to prevent harm

associated with SGLT2i. Larger prospective cohorts describing the characteristics of patients with SGLT2i-associated DKA may improve patient outcomes. This novel case series adds to the limited publications in this area.

Limitations

As a case series, this analysis is prone to usually-associated biases. The sample size affects the generalisability of results, though given the paucity of data in this field any contribution to the evidence is of interest. Data with respect to missed insulin doses or inappropriate dose adjustments limited the analysis in those taking insulin.

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Author contributions

ST, CE, RW and DW collected and reviewed the data for analysis. JS conducted the statistical analysis. ST, CE, RW, DW and JS all contributed to the preparation and review of the manuscript.

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Table and Figures

Legend for Figure 1: Diabetes therapies in addition to SGLT2i on admission with DKA

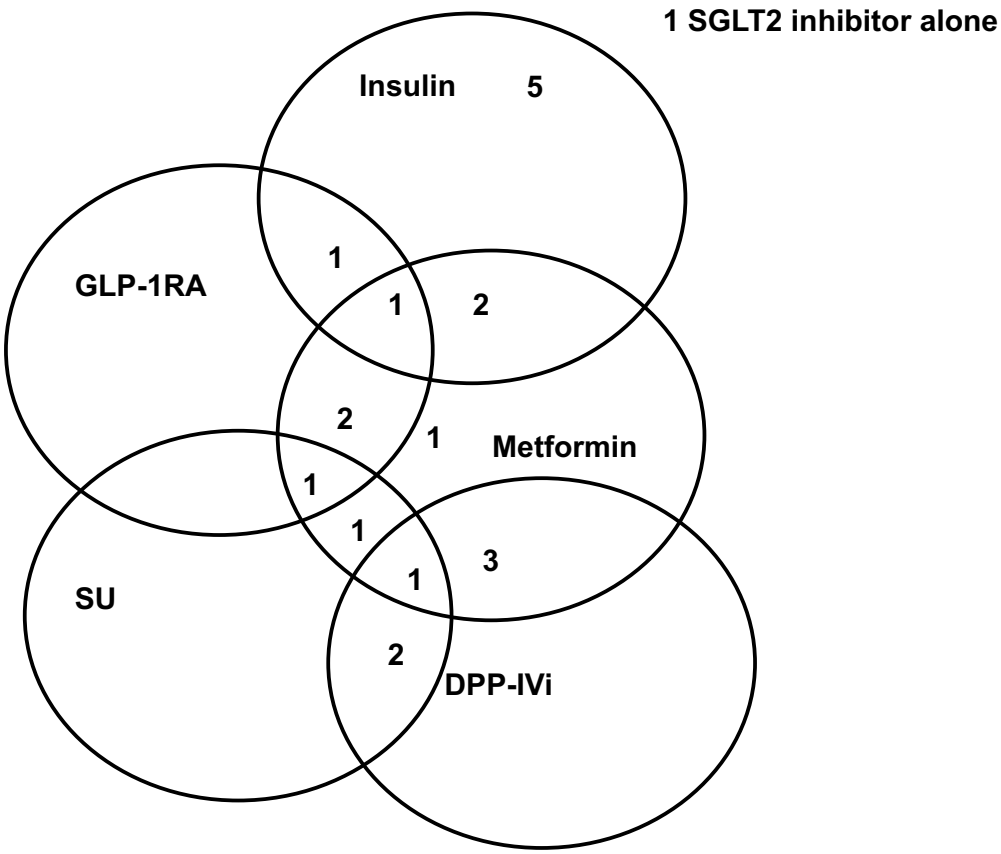
Figure 1 presents the diabetes therapies prescribed to patients admitted with DKA associated with SGLT2i use. Abbreviations: *DPP-IVi* Dipeptidyl Peptidase 4 Inhibitors; *GLP-1RA* Glucagon Like Peptide-1 receptor agonists; *SU* sulphonylurea; *SGLT2i* Sodium-Glucose Cotransporter-2 Inhibitors.

Table 1: Admission characteristics of patients with DKA whilst receiving SGLT2 inhibitors

Numbers (and percentage) are shown for discrete variables. Data are displayed as the mean±standard deviation or as *median (and range). Infection comprise of infective endocarditis, pneumonia, leg abscess). Abbreviations: DKA: Diabetic ketoacidosis; eGFR estimated glomerular filtration rate; HbA1c glycated haemoglobin; SGLT2 sodium-glucose co-transporter-2.

Table 1: Admission characteristics of patients with DKA whilst receiving SGLT2 inhibitors

Characteristics	Number (%) Mean ± standard deviation
Gender (male/female)	13/9 (59.1/40.9%)
Age (years)	60.7±12.2
Type 1/Type 2 diabetes	2/20 (9.1/90.9%)
Duration of diabetes (years)	15.6±8.8
Dapagliflozin/Empagliflozin/Canagliflozin	7/13/2 (31.8/59.1/9.1%)
HbA1c (mmol/mol) [%]	89±29 [10.3%]
Creatinine (µmol/L)	78±26
eGFR (mL/min/1.73 m^2)	79±20
Died/Alive	3/19 (13.6/86.4%)
Length of stay (days)	10.2±7.9, 7.8 (2-38)*
Admission glucose (mmol/L)	23.2±8.8
Admission blood ketone (mmol/L)	4.8±1.3
Admission pH	7.2±0.2
Admission bicarbonate (mmol/L)	11.9±5.6
Admission diagnosis	
DKA alone	10 (45.5%)
DKA & Infection	6 (27.3%)
DKA & Acute coronary syndrome	1 (4.5%)
DKA & COVID-19	4 (18.2%)
DKA & Complete heart block	1 (4.5%)


1 SGLT2 inhibitor alone
Insulin
5
GLP-1RA
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