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# Comparison of Duration of Ketoacidosis in Sodium-Glucose Transport-2 Inhibitor (SGLT2i) Users and Non-Users among Individuals with Type 2 Diabetes: Case Series

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## Abstract

**Background:** Sodium Glucose Transport inhibitors (SGLT2i) are approved for the treatment of diabetes but can lead to a complication known as Diabetic Ketoacidosis (DKA). This study aims to compare the duration of ketoacidosis and metabolic profiles between SGLT2i users and non-users with type 2 diabetes.

**Case Report:** A case series was conducted, including patients admitted with DKA between 2016 and 2022. Data were collected from medical records, and statistical analysis was performed using Microsoft Excel. The Montfort Hospital Research Ethics Board (Institute of Savoir Montfort) approved this study (File number: 21-22-02-040). A total of 88 patients were included, with 55 non-SGLT2i users and 33 SGLT2i users. SGLT2i users had significantly prolonged ketoacidosis mean duration compared to non-users (14.45 h *vs*. 10.93 h, p=0.0001).

**Conclusion:** This retrospective case series of 88 type II diabetes patients admitted with DKA found that SGLT2i users experience significantly longer mean duration of ketoacidosis. Recognizing the risks of prolonged ketoacidosis in critical care settings is crucial, prompting vigilant monitoring and frequent laboratory tests to expedite resolution and improve outcomes. These insights may inform clinical decision-making, potentially reducing ICU stays and improving overall outcomes for individuals with diabetes.

**Keywords: Sodium-glucose transport inhibitors; Diabetic ketoacidosis; Prolonged ketoacidosis; Metabolic profiles; SGLT2i users; Non-SGLT2i users**

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## Introduction

Sodium-Glucose Transport inhibitors (SGLT2i) are approved for the treatment of diabetes and have demonstrated additional benefits in heart failure [1]. However, the use of SGLT2i can lead to a significant complication known as Diabetic Ketoacidosis (DKA). DKA is a rare complication associated with SGLT2i use with reported incidence rates ranging from 0.6 to 2.2 events per 1,000 person-year in studies [2].

Several common triggers have been identified for those taking SGLT2i and who are admitted for DKA, including infection, surgical stress, poor oral intake, dehydration, and increasing insulin requirements [3]. As such, management of SGLT2i use during acute illness presents unique challenges. Case reports have also documented episodes of prolonged ketoacidosis in SGLT2i users [4,5]. Episodes of ketoacidosis are considered prolonged when the resolution extends beyond 24 h [6].

Proposed mechanisms for this prolonged ketoacidosis include the slow dissociation rate (slow off-rate) of SGLT2 inhibition, metabolic enzyme polymorphisms, decreased renal function, and the lipophilicity of certain drugs, such as Canagliflozin [7]. However, beyond the influence of drug-related factors, the extent to which the initial severity of acidosis upon admission might also play a role in extending the duration of acidosis in SGLT2i users remains ambiguous.

Given the unique metabolic complications observed in SGLT2i users admitted with DKA, our

study aims to retrospectively compare the duration of ketoacidosis with that of non-SGLT2i users.

## Methods

A case series was conducted at a community hospital in Ottawa, Ontario, Canada. The inclusion criteria for this study encompassed adult patients aged 18 years and above who were admitted to Montfort Hospital between January 1st, 2016, and June 30th, 2022. Specifically, eligible participants were required to have a documented diagnosis of Diabetic Ketoacidosis (DKA) upon admission, determined by an emergency physician or critical care consultant, and a history or diagnosis of type 2 diabetes mellitus. Additionally, inclusion necessitated the presence of raised Anion Gap (AG) metabolic acidosis (AG>12 mmol/L and Bicarbonate [$HCO_3$] levels <24 mmol/L) upon admission, along with elevated ketones. These criteria were established to ensure the enrollment of patients with DKA attributed to type 2 diabetes mellitus and to standardize the population under investigation for the comparative analysis between SGLT2i users and non-users. Data was collected from electronic medical records and verified by two study investigators.

Duration of ketoacidosis was recorded in hours and defined as the time taken for the anion gap to normalize. Patients were excluded if the prolonged duration of ketoacidosis was due causes other than ketone production (*e.g.* other causes of anion gap acidosis or non-anion gap acidosis). For our primary objective, given the prolonged nature of ketoacidosis episodes lasting beyond 24 h, our aim was to compare the incidence of patients in both groups whose time to anion gap closure extended to 24, 36, and more than 48 h.

Baseline patient characteristics, laboratory data and metabolic profiles were collected for both groups. Patient characteristic data encompassed sex, age, admission weight, home diabetes medication usage, and suspected risk factors for ketoacidosis. Collected admission metabolic and laboratory values included serum creatinine, random blood glucose, pH, bicarbonate, anion gap, beta-hydroxybutyric acid, and Hemoglobin A1C (HbA1c) percentage. Mean values for all laboratory parameters were documented and compared between SGLT2i users and non-users.

### Data collection

The data for this study was collected from de-identified patient records at Montfort Hospital, spanning the period from January 01st, 2016, to June 30th, 2022. Deidentification measures were implemented to ensure the removal of any personally identifiable information, thereby safeguarding patient confidentiality. The collected data encompassed demographic information, patient histories, diabetes control markers including metabolic parameters, and relevant laboratory data including time to anion gap closure measured in hours. The deindexed records were utilized for statistical analysis, ensuring the protection of patient privacy and compliance with ethical standards.

### Statistical analysis

Baseline patient characteristics were described using a combination of continuous and categorical variables. Continuous variables were utilized to depict the primary objective, focusing on the time to anion gap closure measured in hours, comparing SGLT2i users and non-users. To analyze the primary objective, independent sample t-tests were initially employed to compare the duration of ketoacidosis, measured as time to anion gap closure, between SGLT2i users and non-SGLT2i users, with consideration given to data normality assumptions. Additionally, the metabolic profiles were summarized using continuous variables, representing mean values at admission for both groups. We chose a significance level of 5% ($p<0.05$) as the threshold for statistical significance, as this is a commonly accepted standard in scientific research. No adjustment for multiple tests was performed, as no single adjustment is widely accepted. All statistical analyses were conducted using Microsoft Excel 2022.

## Results

A total of 88 patients with type 2 Diabetes Mellitus (DM) were admitted with DKA between January 01st, 2016, and June 30th, 2022, and were included in this study. Among these patients, 55 individuals did not use SGLT2i at presentation, while 33 patients were taking SGLT2i immediately prior to admission with DKA. The SGTL2i and non-SGLT2i groups had similar sex, age, and weight distributions (Table 1). On admission, the non-SGLT2i group exhibited higher mean blood glucose levels than the SGLT2i group (38.1 mmol/L *vs.* 22.1 mmol/L), as well as an increased mean anion gap (28.34 *vs.* 24.81), and hemoglobin A1C percentage (12% *vs.* 10.4%). There was no difference in admission mean creatinine between non-SGLT2i

**Table 1:** Baseline characteristics and admission metabolic profiles of non-SGLT2i *vs.* SGTL2i users admitted with DKA.

| | Non-SGLT2i users (n=55) | SGLT2i users (n=33) |
|---|---|---|
| **Sex** | | |
| Male (%) | 51 | 55 |
| Female (%) | 49 | 45 |
| Age – mean (years) | 55.6 ± 4.4 | 54.1 ± 4.8 |
| Weight – mean (kilograms) | 82.6 ± 6 | 89.6 ± 5 |
| Creatinine (umol/L) | 133 ± 24 | 124 ± 23 |
| Admission Blood Glucose – mean (4-10 mmol/L) | 38.1 ± 4.3 | 22.1 ± 4.1 |
| pH – mean (7.35-7.45) | 7.11 ± 0.03 | 7.15 ± 0.03 |
| Bicarbonate – mean (22-27 mmol/L) | 10.46 ± 1.56 | 10.92 ± 1.56 |
| Anion Gap – mean (8-16 mmol/L) | 28.34 ± 2.16 | 24.81 ± 2.09 |
| Beta-hydroxybutyric acid (mmol/L) (<= 0.27) – mean | 8.31 ± 0.95 | 7.68 ± 0.95 |
| Hemoglobin A1C% - mean (4.8-5.9%) | 12.05 ± 0.53 | 10.41 ± 0.78 |
| **Medications** | | |
| Insulin (%) | 24 (44) | 8 (24) |
| Biguanide (%) | 17 (31) | 28 (85) |
| Sulfonylurea (%) | 8 (15) | 10 (30) |
| DPP-4 Inhibitor (%) | 7 (13) | 11 (33) |
| GLP-1 agonist (%) | 0 | 3 (9) |
| **Risk factors for ketoacidosis** | | |
| Non-compliance (%) | 22 (40) | 9 (27) |
| New onset diabetes (%) | 17 (31) | 0 |
| Dehydration (%) | 9 (16) | 16 (49) |
| Infection (%) | 5 (9) | 6 (18) |
| Surgical stress (%) | 1 (2) | 0 |
| Pancreatitis (%) | 1 (2) | 0 |
| Low carb/keto diet (%) | 0 | 2 (6) |

DKA: Diabetic Ketoacidosis; SGLT2i: Sodium-Glucose Transport-2 inhibitor user; Non-SGLT2i: Sodium-Glucose Transport-2 inhibitor non-user

**Table 2:** Duration of ketoacidosis during DKA admissions in non-SGLT2i users *vs.* SGLT2i users.

| | Non-SGLT2i users (n=55) | SGLT2i users (n=33) | p-value |
|---|---|---|---|
| Time to anion gap closure – mean (hours) | 10.93 ± 2.01 | 14.45 ± 3.73 | 0.0001 |
| Number of patients with time to anion gap closure >24 h (% of patients) | 1 (1.8) | 5 (15) | |
| Number of patients with time to anion gap closure >36 h (% of patients) | 0 | 2 (6) | |
| Number of patients with time to anion gap closure >48 h (% of patients) | 0 | 1 (3) | |

DKA: Diabetic Ketoacidosis; SGLT2i: Sodium-Glucose Transport-2 inhibitor user; Non-SGLT2i: Sodium-Glucose Transport-2 inhibitor non-user

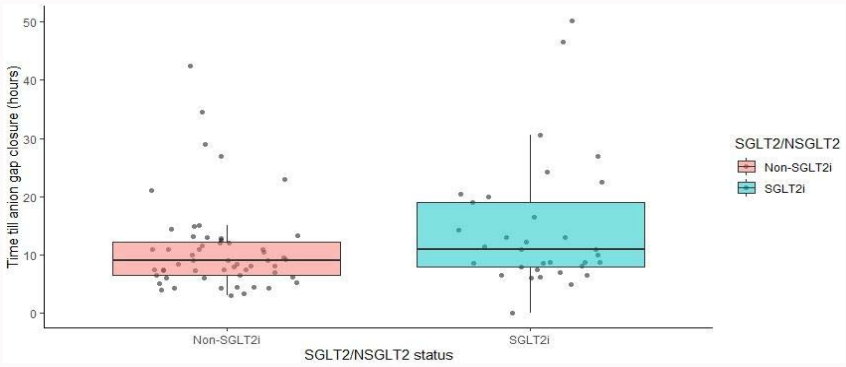


**Figure 1:** Distribution of length to anion gap closure in hours in non-SGLT2i users *vs.* SGLT2i users.

and SGLT2i users (133 mmol/L *vs.* 124 mmol/L). The non-SGLT2i group exhibited a greater prevalence of insulin usage (44% *vs.* 24%) alongside a lower prevalence of biguanide utilization (31% *vs.* 85%) compared to SGLT2i users. The two groups also had differing rates of documented risk factors for ketoacidosis, with non-compliance to medication the predominant risk factor in the non-SGLT2i group, accounting for 40% of cases, whereas dehydration was the leading risk factor among the SGLT2i group, with a prevalence of 49% (Table 1).

Significantly prolonged duration of ketoacidosis was observed in the SGLT2i group compared to the non-SGLT2i group (14.45 h *vs.* 10.93 h, p=0.0001) (Table 2). Within the SGLT2i group, five patients failed to resolve their anion gap within 24 h of admission, whereas only one patient in the non-SGLT2i group experienced prolonged ketoacidosis. Notably, among the five patients with prolonged ketoacidosis exceeding 24 h in the SGLT2i user group, one patient required 46.5 h, while another patient required 50.2 h for their anion gap to normalize, surpassing the respective thresholds of 36 and 48 h (Table 2 and Figure 1).

## Discussion

This case series identified prolonged duration of ketoacidosis in SGLT2i users compared to non-SGLT2i users with type 2 DM admitted with DKA. The mean duration of acidosis, measured as the time to anion gap closure, was prolonged in SGLT2i users compared to non-SGLT2i users. Out of the 33 SGLT2i users, five patients experienced prolonged ketoacidosis with an open anion gap lasting over 24 h. Remarkably, within the subset of five patients experiencing ketoacidosis for over 24 h in the SGLT2i group, two cases were particularly prolonged, with one patient taking 46.5 h and another 50.2 h for anion gap normalization, significantly exceeding durations of 36 and 48 h respectively.

SGLT2i induce ketoacidosis primarily through glycosuria, where the drugs' inhibition of glucose reabsorption in the kidneys leads to reduced blood glucose levels and subsequent insulin deficiency. This scarcity of insulin prompts the body to shift its energy source to lipids (lipid oxidation) and non-carbohydrate compounds (gluconeogenesis), resulting in the production of ketone bodies as by-products. Furthermore, the escalation in glucagon secretion, which antagonizes insulin, enhances hepatic glucose and ketone production, thereby intensifying the ketoacidotic condition [8].

In addition, SGLT2i impede the kidney's ability to clear ketone bodies by enhancing their reabsorption in the renal tubules. This effect stems from the drugs' inhibition of sodium reabsorption, leading to elevated sodium concentrations in the tubular fluid. Consequently, the heightened sodium levels facilitate the carrier-mediated reabsorption of negatively charged ketone bodies, contributing to their accumulation in the body [9].

In summary, the interaction of various mechanisms, including glycosuria-induced insulin deficiency, changes in energy metabolism promoting lipid oxidation and gluconeogenesis, elevated glucagon levels, and improved tubular reabsorption of ketones, fosters an environment conducive to the production and accumulation of ketone bodies. This process ultimately increases the risk of ketoacidosis in individuals using SGLT2 inhibitors.

When examining the metabolic profiles between the non-SGLT2i and SGLT2i users, there was a modestly higher anion gap observed in the non-SGLT2i group. Other metabolic parameters for acidosis such as pH and bicarbonate levels appeared to be similar between both groups. It is worth considering whether the discrepancy in anion gap elevation observed could be associated with the underlying causes of admission and precipitating factors of Diabetic Ketoacidosis (DKA) episodes. Within the non-SGLT2i group, the prevalence of non-compliance and new-onset diabetes suggests potentially inadequate baseline control before hospitalization. This notion is supported by a comparison of admission elevated blood glucose and HbA1c percentages between the two groups, indicating less stringent glucose control in the non-SGLT2i user group. Another noteworthy observation pertains to the prevalence of insulin usage

within the SGLT2i group, accounting for 24% of admissions in this cohort. Considering the potential synergistic effect of insulin and SGLT2i in elevating the risk of ketoacidosis, it remains uncertain to what extent insulin usage contributed to the prolonged episodes of ketoacidosis observed in the SGLT2i user group. Nevertheless, a deeper investigation is warranted to elucidate the interplay among precipitating factors, the extent of acidosis severity, and their impact on the duration of ketoacidosis episodes.

Considering that non-SGLT2i users exhibited a higher mean anion gap compared to SGLT2i users, despite experiencing a shorter duration of ketoacidosis, this observation may imply the involvement of additional underlying mechanisms, such as genetic factors and pharmacokinetic characteristics [10]. Regarding genetic factors, Dapaglifozin, Empagliflozin, and Canagliflozin undergo hepatic metabolism and renal excretion. The influence of genetic polymorphisms in the SLC5A2 gene, which encodes SGLT2 transporter expression, remains uncertain in affecting drug action [11]. Similarly, genetic variability in drug-metabolizing enzymes involved in the glucuronidation pathway may impact SGLT2i metabolism, yet no clinical studies have explored these factors' effects on pharmacokinetics or outcomes [12].

Moreover, the pharmacokinetic characteristics of SGLT2i, such as their slow dissociation rate or "slow off-rate," enable sustained pharmacodynamic effects even at low plasma concentrations, possibly explaining persistent ketone reabsorption post-drug discontinuation [13]. Notably, Canagliflozin's lipophilicity may affect its pharmacokinetics, particularly in patients with increased adiposity, leading to alterations in volume of distribution and elimination half-life [14]. Empagliflozin's high selectivity for SGLT2 over SGLT1 underscores its emphasis on urinary glucose excretion, potentially influencing its therapeutic effects [15].

As highlighted earlier, while DKA represents a rare adverse event associated with SGLT2i, it's crucial to maintain perspective on the overall risk-benefit profile of these medications. For the vast majority of patients, the benefits of SGLT2i therapy typically outweigh the risk of DKA. However, it's essential for prescribers to remain vigilant, particularly in certain patient populations where the risk may be elevated. Previously identified risk factors associated with an elevated risk of DKA when using SGLT2 inhibitors encompass underlying medical conditions, recent surgical procedures, decreased carbohydrate consumption, dehydration, and excessive alcohol intake. By carefully considering these factors and monitoring patients appropriately, prescribers can effectively mitigate the risk of DKA while harnessing the therapeutic benefits of SGLT2i.

Specifically in the critical care setting, the understanding of the potential risks associated with prolonged ketoacidosis in SGLT2i users' holds critical clinical implications for intensivists, ultimately influencing the urgent care provided to these individuals. It is crucial to recognize that metabolic factors, including kidney function and the severity of acidosis, may not serve as reliable indicators for predicting prolonged acidosis episodes in SGLT2i users. It is recommended to monitor the acid-base status of patients over an extended duration due to the inherent risk of prolonged ketoacidosis in SGLT2i users and the potential for re-opening of the anion gap. This approach may include more frequent laboratory tests, extended continuous intravenous insulin infusion, and meticulous monitoring of acid-base status to expedite the resolution of acidosis and potentially mitigate the duration of ICU stays.

While the present case series provides valuable insights, several limitations should be acknowledged. Firstly, the retrospective design introduces potential biases, as data collection relies on identification, reporting, and documentation, which may be subject to inconsistencies across time and individual clinicians. The timing of anion gap measurements could have influenced the assessment of the duration of acidosis. Additionally, other potential causes of acidosis were not consistently ruled out, which could have impacted the measurements of the duration of acidosis. Employing creatinine to gauge kidney function and hemoglobin A1C percentage as an indicator of diabetes management might not consistently yield precise results, as they can be affected by a range of unmeasured factors. Lastly, due to resource costs and data availability, this case series solely captured metabolic complications related to SGLT2i usage upon admission and did not consider complications that may have arisen during the hospitalization period.

Considering these limitations, future research endeavors should aim to address these gaps by employing prospective study designs and implementing more rigorous standardized protocols for data collection. Furthermore, investigations exploring the long-term effects and outcomes of prolonged ketoacidosis in SGLT2i users (*e.g.* ICU length of stay) would contribute to a more comprehensive understanding of this clinical entity.

## Conclusion

In summary, this retrospective study involving 88 patients with type 2 diabetes mellitus admitted with Diabetic Ketoacidosis (DKA) between January 01$^{st}$, 2016, and June 30$^{th}$, 2022, demonstrated a longer mean duration of acidosis in SGLT2i users compared to non-users. The interaction of various mechanisms, including glycosuria-induced insulin deficiency, altered energy metabolism favoring lipid oxidation and gluconeogenesis, increased glucagon levels, and enhanced tubular reabsorption of ketones, may increases the risk and duration of ketoacidosis in SGLT2i users. Furthermore, unmeasured genetic variations in metabolic enzyme polymorphisms and drug-specific factors such as low dissociation rate, lipophilicity, and SGLT2 transporter binding affinity may contribute to prolonged episodes of ketoacidosis in these users.

The implications extend to clinical decision-making in critical care settings, where healthcare professionals must recognize the risks associated with prolonged ketoacidosis in SGLT2i users. Monitoring acid-base status over an extended duration and implementing frequent laboratory tests can aid in expediting the resolution of acidosis and improving patient outcomes.

By incorporating these insights and contributing to the growing body of knowledge, we can enhance our understanding of prolonged ketoacidosis in SGLT2i users, leading to improved clinical decision-making, enhanced patient care, possibly mitigating episodes of prolonged duration of ICU stays and ultimately better outcomes for individuals with diabetes.

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