The effect of preoperative sodium-glucose cotransporter 2 inhibitors on the incidence of perioperative metabolic acidosis: A retrospective cohort study

Yudai Iwasaki (yudai.i0213@gmail.com)
Tohoku University Hospital: Tohoku Daigaku Byoin https://orcid.org/0000-0002-0702-0392
Yusuke Sasabuchi
Jichi Medical University: Jichi Ika Daigaku
Sho Horikita
Jichi Ika University Saitama Medical Center: Jichi Ika Daigaku Fuzoku Saitama Iryo Center
Taku Furukawa
Jichi Ika University Saitama Medical Center: Jichi Ika Daigaku Fuzoku Saitama Iryo Center
Junji Shiotsuka
Jichi Ika University Saitama Medical Center: Jichi Ika Daigaku Fuzoku Saitama Iryo Center
Alan Kawarai Lefor
Jichi Ika University Saitama Medical Center: Jichi Ika Daigaku Fuzoku Saitama Iryo Center
Masamitsu Sanui
Jichi Ika University Saitama Medical Center: Jichi Ika Daigaku Fuzoku Saitama Iryo Center

Research Article

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Abstract

Background

Sodium-glucose cotransporter 2 inhibitors (SGLT2-is) are a novel class of anti-hyperglycemic agents. Although several cases of perioperative euglycemic diabetic ketoacidosis have been linked to these medications, the association remains unclear. This study aimed to examine the association between SGLT2-i use and the incidence of perioperative metabolic acidosis with euglycemia, the surrogating outcome of perioperative euglycemic diabetic ketoacidosis.

Methods

This was a retrospective, matched cohort study, which was conducted in the intensive care unit of a tertiary care facility in Japan. We identified patients aged 20 years or older with diabetes mellitus who received pharmacologic therapy and were admitted to the intensive care unit after elective surgery between April 2014 and March 2019. We extracted the following data from the electronic medical records for matching: age, sex, surgery year, surgical site, hemoglobin A1c level, and prescription for SGLT2-is. Eligible patients were divided into two groups, those who were prescribed SGLT2-is (SGLT2-I group) and those who were not (control group). For each patient in the SGLT2-i group, we randomly selected four patients from the control group matched for the extracted characteristics. The primary outcome was the incidence of metabolic acidosis with an elevated anion gap and euglycemia. The secondary outcome was the lowest pH value of each patient during their intensive care unit stay.

Results

A total of 155 patients were included in this study. Patients receiving SGLT2-is had comparable characteristics to the control participants; however, the proportions of patients undergoing dialysis were not similar. Metabolic acidosis with euglycemia was seen in 7/31 (22.6%) patients receiving SGLT2-is and in 10/124 (8.1%) control patients ($p = 0.047$).

Conclusions

This study shows that the use of SGLT2-is is associated with a significantly higher incidence of metabolic acidosis with euglycemia. Patients receiving SGLT2-is who are scheduled to undergo invasive surgical procedures should be closely monitored for the development of euglycemic diabetic ketoacidosis.

Background

Diabetes mellitus is present in approximately 10–15% of patients who undergo surgical procedures and is a global public health challenge [1, 2]. Several pharmacologic agents have been recently developed to control diabetes mellitus. Sodium-glucose cotransporter 2 inhibitors (SGLT2-is) are a novel class of anti-hyperglycemic agents. SGLT is present in the proximal tubule of the kidney and functions as a cotransporter of sodium and glucose from the blood to the urine. The hypoglycemic effect of SGLT2-is is exerted by inhibiting SGLT [3]. SGLT2-is are recommended as second-line drugs in the Canadian guidelines for the treatment of patients with diabetes mellitus [4]. Currently, the use of SGLT2-is is increasing worldwide, including in Japan.

Although SGLT2-is have several organ-protective effects [5, 6], they are associated with an increased incidence of side effects, including dehydration, dry mouth, urinary tract infections, and euglycemic diabetic ketoacidosis (eDKA), the most severe adverse effect of the drug. eDKA has been reported to occur in patients using SGLT2-is by increasing glucagon, which promotes ketogenesis and lipolysis in the liver, ultimately resulting in glucose release into the urine [7].

eDKA has been reported in approximately 0.1% of patients who use SGLT2-is [8] and eDKA is considered to be a rare complication. Nonetheless, there are several case reports of perioperative eDKA likely associated with SGLT2-i use. A systematic review of perioperative diabetic ketoacidosis reported 42 patients with eDKA in the perioperative period [9]. However, this systematic review included only case reports or case series and did not provide epidemiological evidence of an association between SGLT2-i use and perioperative eDKA. Furthermore, ketoacidosis has been reported in 3% of critically ill patients with diabetes mellitus [10], suggesting that it may occur because of diabetes mellitus itself rather than because of the prescribed medication. It remains unclear whether the use of SGLT2-is is associated with perioperative ketoacidosis.

In this study, we aimed to evaluate whether SGLT2-i use is associated with the incidence of perioperative diabetic ketoacidosis. We hypothesized that the use of SGLT2-is would be associated with an increased incidence of eDKA.

Methods

Study design and patient population

This retrospective matched-pair cohort study was conducted in the intensive care unit (ICU) of Saitama Medical Center of Jichi Medical University, a tertiary care facility in Japan. Approximately 2000 patients are admitted annually to this ICU. This study was approved by the Jichi Medical University Bioethics Committee, the review board of this hospital, on March 24, 2020 (full board name: Jichi Medical University Bioethics Committee for Clinical Research, Saitama Medical Center; approval number: S19-156). This study adhered to the principles of the Declaration of Helsinki. The requirement for written consent was waived because of the retrospective study design.

Patient selection

Patients aged 20 years or older with type 1 or type 2 diabetes mellitus who were admitted to the ICU after elective surgery between April 2014 and March 2019 were identified. Patients who underwent emergency surgery or surgery with cardiopulmonary bypass were excluded. Subsequently, patients receiving pharmacological therapy for diabetes mellitus were selected. The pharmacological therapy status was confirmed when at least one antidiabetic drug was prescribed. Data regarding the following characteristics were extracted from the electronic medical records: age, sex, surgery year, surgical type (cardiovascular, respiratory, urological, neurosurgery, abdominal, or orthopedic surgery), hemoglobin A1c (HbA1c) level, and SGLT2-i prescription.

One to four pair matching of patients using SGLT2-is and patients not using SGLT2-is

Eligible patients were divided into two groups: those were using SGLT2-is (SGLT2-i group) preoperatively and those who were not (control group). For each patient in the SGLT2-i group, four patients of the same sex, age category (≦ 49, 50–59, 60–69, 70–79, and ≧ 80 years old), year of surgery (2014, 2015, 2016, 2017, 2018, and 2019), surgery type, and HbA1c category (HbA1c < 6%, ≧ 6% and < 7%, ≧ 7% and < 8%, ≧ 8% and < 9%, and ≧ 9%) were randomly selected from the control group and matched. In this hospital, SGLT2-is were stopped on the day of surgery during the study period.

Data collection

The following characteristics were reviewed for matched patients: sex; weight; height; body mass index; Acute Physiology and Chronic Health Evaluation II (APACHE II) scores; [11] surgery year; surgical type; HbA1c level; type of SGLT2-is; use of other antidiabetic drugs; serum creatinine; estimated glomerular filtration rate (eGFR) calculated by the GFR equation for the Japanese population; [12] and history of cancer, hypertension, heart failure, myocardial infarction, stroke, peripheral arterial disease, and dialysis. In this ICU, arterial blood gas analysis was performed 3–6 times daily for each patient; we included the arterial blood gas analysis data collected during the patients' ICU stay.

The primary outcome was the incidence of metabolic acidosis with an elevated anion gap and euglycemia during the ICU stay. The primary aim was to evaluate the incidence of eDKA. However, since blood ketone and urine ketone body levels were not measured, the outcome of interest was the incidence of metabolic acidosis with a high anion gap and euglycemia instead of the incidence of eDKA. The definition of this outcome was pH < 7.3, anion gap of > 12 mmol/L, $PaCO_2$ < 45 mmHg, and glucose levels of < 252 mg/dL, based on previously reported values [13]. We did not include lactate levels of > 5 mmol/L as the primary outcome, as these values suggest lactic acidosis, not eDKA [14]. The secondary outcome was the lowest pH value for each patient during the ICU stay.

Statistical analysis

Normally distributed continuous variables are reported as the mean and standard deviation, whereas non-normally distributed continuous variables are reported as the median with the first and third quartiles. Categorical variables are reported as counts and percentages. After one-to-four matching, characteristics

were compared between the groups. Normally and non-normally distributed continuous variables were compared using the *t*-test and Man–Whitney U test, respectively. Categorical variables were compared using Fisher's exact test. Two-sided p-values of < 0.05 were considered statistically significant.

Multivariable linear regression analysis was conducted to evaluate whether SGLT2-i use was associated with the lowest pH during the ICU stay. The following factors were included in the model: binary variables of SGLT2-i use, insulin use, metformin use, and dialysis induction; the categorical variable of surgery type; and continuous variables of eGFR, age, duration of surgery, APACHE2 score, and HbA1c levels. These factors were selected according to their clinical impact on outcomes.

Subgroup analysis was conducted by excluding patients with end-stage kidney disease, which was defined as an eGFR of ≤ 30 ml/min/1.73m^2. Multiple imputation was scheduled to be conducted if the proportion of missing data was ≥ 5% [15]. If the proportion of missing data was < 5%, the listwise deletion method was used.

Results

A total of 751 patients were screened for this study. Two hundred and eighty-four patients were excluded because they did not receive pharmacological therapy for diabetes mellitus, and the remaining 467 patients were eligible for inclusion. After matching, 155 patients were included (Fig. 1). The patient characteristics are presented in Additional file 1. The proportions of patients that underwent dialysis or presented preoperatively with myocardial infarction were significantly different between the two groups, and there were no significant between-group differences in other parameters. Empagliflozin was used for 24 patients in the SGLT2-i group and was the most frequently used SGLT-i. All patients stopped using SGLT2-is on the day of surgery.

The parameters of interest are presented in Table 1. A total of 1527 blood gas analyses were conducted in this cohort. Twenty blood gas analyses showed evidence of lactic acidosis (SGLT2-i group: 2 patients and 7 readings; control group: 6 patients and 13 readings) and were excluded from the analysis of the primary outcome. Analyses of blood gas data for the lowest pH value in each patient revealed missing lactate level data in four (2.5%) patients. Therefore, we performed listwise method analysis. All other data were complete. Metabolic acidosis with euglycemia occurred in 7/31 and 10/124 (22.6% vs. 8.1%, p = 0.047) patients in the SGLT2-i and control groups, respectively. The ICU length of stay was comparable in both groups. Bicarbonate levels, base excess, and anion gap values were significantly different between the two groups.

Table 1
Comparison of perioperative outcomes

Outcomes	SGLT2-i (n = 31)	Matched Controls (n = 124)	*p*-value
Metabolic acidosis with euglycemia, n, (%)	7 (22.6)	10 (8.1)	**0.047**
ICU stay, hours, median [IQR]	43.00 [21.00, 47.50]	22.00 [18.00, 49.00]	0.061
Blood gas analysis of the lowest pH at ICU admission			
Lowest pH, median [IQR]	7.33 [7.30, 7.36]	7.35 [7.31, 7.38]	0.12
$PaCO_2$, mmHg, median [IQR]	41.00 [36.00, 44.65]	43.45 [39.88, 47.02]	**0.013**
Glucose, mg/dL, median [IQR]	147.00 [123.00, 174.50]	161.50 [124.75, 201.25]	0.19
Lactate, mmol/L, median [IQR]	1.39 [1.15, 1.81]	1.30 [1.08, 1.80]	0.71
Sodium, mEq/L, median [IQR]	137.00 [134.80, 138.10]	135.95 [134.17, 137.60]	0.22
Potassium, mEq/L, median [IQR]	4.28 [3.88, 4.54]	4.08 [3.86, 4.30]	0.15
Chloride, mEq/L, mean (SD)	106.19 (4.06)	104.94 (3.23)	0.068
Bicarbonate, mEq/L, median [IQR]	22.00 [18.55, 23.20]	23.35 [21.70, 24.90]	**< 0.001**
Base excess, mmol/L. median [IQR]	-3.70 [-8.00, -2.05]	-2.55 [-3.90, -0.85]	**0.002**
Anion gap, mEq/L, median [IQR]	14.20 [11.45, 16.75]	11.65 [9.60, 13.50]	**0.004**

Abbreviation: ICU = intensive care unit, IQR = interquartile range, $PaCO_2$ = partial pressure of arterial carbon dioxide, SD = standard deviation, SGLT2-i = sodium-glucose cotransporter 2 inhibitor

Significant *p*-values ($p < 0.05$) are in bold.

Additional file 2 and Table 2 present the results of the subgroup analyses. The subgroups, excluding patients with end-stage kidney disease, included 27/31 and 95/124 patients in the SGLT2-i and control groups, respectively. There were three (2.4%) cases of missing lactate level data in these subgroups, and the listwise deletion method was used. Patient baseline characteristics were comparable in both groups, except for the frequency of preoperative heart failure. The difference in the incidence of acidosis between the two groups was more pronounced in the subgroup analysis than in the main analysis.

Table 2
Comparison of perioperative outcomes (excluding patients with severe chronic kidney disease)

Outcomes	SGLT2-i (n = 27)	Matched Controls (n = 95)	*p*-value
Metabolic acidosis with euglycemia, n (%)	6 (22.2)	6 (6.3)	**0.024**
ICU stay, hours, median [IQR]	23.00 [21.00, 47.50]	22.00 [18.00, 54.50]	0.15
Blood gas analysis of the lowest pH at ICU admission			
Lowest pH, median [IQR]	7.33 [7.30, 7.36]	7.35 [7.32, 7.38]	0.11
$PaCO_2$, mmHg, median [IQR]	40.20 [36.00, 44.35]	44.00 [40.05, 46.90]	**0.002**
Glucose, mg/dL, median [IQR]	144.00 [119.50, 171.00]	164.00 [133.50, 203.00]	**0.027**
Lactate, mmol/L, median [IQR]	1.41 [1.10, 1.81]	1.31 [1.08, 1.86]	0.94
Sodium, mEq/L, median [IQR]	137.20 [135.10, 138.35]	136.20 [134.45, 137.90]	0.20
Potassium, mEq/L, median [IQR]	4.14 [3.76, 4.52]	4.05 [3.88, 4.24]	0.31
Chloride, mEq/L, mean (SD)	106.59 (4.02)	105.23 (3.29)	0.074
Bicarbonate, mEq/L, median [IQR]	22.00 [18.55, 23.20]	23.70 [22.60, 25.10]	**< 0.001**
Base excess, mmol/L. median [IQR]	-3.70 [-6.90, -2.05]	-2.20 [-3.45, -0.55]	**< 0.001**
Anion gap, mEq/L, median [IQR]	13.30 [11.45, 16.55]	10.70 [9.10, 12.50]	**0.002**

Abbreviation: ICU = intensive care unit, IQR = interquartile range, $PaCO_2$ = partial pressure of arterial carbon dioxide, SD = standard deviation, SGLT2-i = sodium-glucose cotransporter 2 inhibitor

Significant *p*-values ($p < 0.05$) are in bold.

Additional file 3 shows the results of the multivariable linear regression analysis of factors associated with the lowest pH during the ICU stay. In addition to P_aCO_2 and anion gap values, SGLT2-i use, duration of surgery, and the APACHE2 score were independently associated with the lowest pH during the ICU stay. Among drugs included in the model, only SGLT2-is were associated with pH in this analysis (coefficient: -0.026, 95% confidence interval: -0.041 to -0.01, $p < 0.01$).

Discussion

In this study, we investigated the incidence of postoperative metabolic acidosis after elective surgery in patients with diabetes mellitus; specifically, we compared the incidence in patients treated with SGLT2-is to the incidence in those who were not. We found that preoperative use of SGLT2-is was associated with an increased incidence of metabolic acidosis without hyperglycemia during the ICU stay after elective surgery. The results of the multivariable linear regression analysis suggested that SGLT2-is were the only type of medication that affected pH among the medications included in the model. Although we could only detect the incidence of metabolic acidosis with euglycemia, these results suggest that perioperative SGLT2-i use is associated with eDKA—one of the major causes of mortality among patients with diabetes [16].

To the best of our knowledge, this was the first study to evaluate the relationship between the preoperative use of SGLT2-is and the incidence of perioperative metabolic acidosis. A previous systematic review suggested that perioperative eDKA is a common condition in patients treated with SGLT2-is [9]. However, since that systematic review only included case reports or case series, the relationship between eDKA and SGLT2-is remained unclear. In the present study, we performed an adjustment for confounding factors using one-to-four matching for patients treated with an SGLT2-i and controls. We found an association between SGLT2-i use and an increased incidence of postoperative metabolic acidosis. A previous study showed that patients are exposed to food deprivation and dehydration during the perioperative period, and thus they may be vulnerable to developing eDKA [17].

In this study, both groups had a high incidence of metabolic acidosis compared to that reported in a previous study [10]. Two reasons may explain the high incidence of metabolic acidosis in this study. First, the study hospital is among the leading cardiovascular centers in Japan, and approximately half of the patients in this study underwent cardiovascular surgery, which is an invasive surgical procedure. Stress induced by the surgical procedure may increase the incidence of metabolic acidosis [18]. Second, in this study, patients stopped receiving SGLT2-is on the day of surgery to decrease the risk of perioperative eDKA [17]. The Japanese package inserts distributed with prescription drugs recommend that these drugs be stopped on the day of surgery. The patients in this study followed these recommendations. In contrast, the United States Food and Drug Administration (USFDA) recommends that this drug be stopped 3 or 4 days before surgery [19]. The patients in this study had a withdrawal period that was shorter than that of patients following the USFDA recommendation. The short withdrawal period may have increased the incidence of metabolic acidosis identified in this study.

These findings suggest that meticulous perioperative monitoring of arterial blood gas results may be needed in patients with diabetes mellitus who are treated with SGLT2-is. Patients who undergo highly invasive procedures (e.g., cardiovascular surgery) may be at a higher risk of developing eDKA. Withdrawal of medication on the day of surgery may be insufficient to prevent eDKA.

This study had several limitations. First, we did not examine the level of ketone bodies in the patients' blood or urine. The ICU did not conduct routine urinalyses, and measurement of ketone bodies in the blood is difficult in Japanese hospitals because the required devices are not covered by the national

insurance system. Therefore, we assessed the incidence of metabolic acidosis without accounting for hyperglycemia. However, ketoacidosis is among the common causes of a high anion gap in patients with metabolic acidosis [20]. These results provide preliminary evidence of an association between SGLT2-i use and the incidence of perioperative eDKA. Second, there were differences in the proportions of patients in the two groups who had undergone dialysis and those who presented with cardiovascular disease. SGLT2-i use may reduce the incidence of cardiovascular events [5, 21, 22] and help prevent decline in renal function [6, 22–24]. SGLT2-is may not be used to treat patients with anuria because the drug affects the proximal tubule of the kidney and promotes glucose excretion. The characteristics of this drug may account for the differences between the study groups. The electronic database did not include information on eGFR, dialysis, or history of cardiovascular disease. This limitation of the dataset may have introduced some selection bias to this study. However, a subgroup analysis of patients without chronic kidney disease showed larger between-group differences for the primary outcome, suggesting that the overall findings were robust. Third, the external validity of this study remains unclear. In December 2020, the Japan Diabetes Society recommended a preoperative withdrawal period of SGLT2-is to match that of the USFDA guideline [25]. However, in this study, the patients did not stop using SGLT2-is 3 or 4 days before surgery. This delay in withdrawal might have affected the incidence of metabolic acidosis. Further studies are required to estimate the incidence of ketoacidosis in contexts where an appropriate withdrawal period is observed. A multicenter observational study examining the incidence of postoperative ketoacidosis associated with SGLT2-i use is on-going in Japan [26].

Conclusions

This study showed that the use of SGLT2-is is associated with an increased incidence of metabolic acidosis with euglycemia. Patients receiving SGLT2-is who are scheduled to undergo invasive surgical procedures should be closely monitored with blood gas analysis for the development of eDKA, especially those with a short interval between the surgery and withdrawal of these medications.

Abbreviations

APACHE II, Acute Physiology and Chronic Health Evaluation II

eDKA, euglycemic diabetic ketoacidosis

eGFR, estimated glomerular filtration rate

HbA1c, hemoglobin A1c

ICU, intensive care unit

SGLT2-i, sodium-glucose cotransporter 2 inhibitor

Declarations

Ethics Approval and Consent to Participate

This study was approved by the Jichi Medical University Bioethics Committee for Clinical Research at Saitama Medical Center on March 24, 2020 (approval number: S19-156). The requirement for written consent was waived because of the retrospective study design.

Consent for Publication

Not applicable.

Availability of Data and Material

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing Interests

The authors declare that they have no competing interests.

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None.

Authors' Contributions

All authors contributed to the study design. Data collection was performed by YI, SH, and TF. Analysis was performed by YI and YS. The first draft of the manuscript was written by YI and all authors commented on and revised the versions of the manuscript. All authors read and approved the final manuscript.

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Figures

Figure 1

Flowchart of screening and matched-pair selection of patients with diabetes who underwent elective surgery.

SGLT2 inhibitor = sodium-glucose cotransporter-2 inhibitor

Supplementary Files

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