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RESEARCH LETTER

Concurrent SGLT2 inhibitor use in patients with type 2 diabetes hospitalised for high-dose corticosteroid therapy: Mitigated iatrogenic hyperglycaemia

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1 | BACKGROUND

High-dose corticosteroid therapy is vital for anti-inflammation or immunosuppression in certain diseases but often causes hyperglycaemia, treated with insulin injections.[1] Steroid-induced hyperglycaemia can result from both high-dose and consistent low- to intermediate-dose corticosteroids. Approximately 10%–15% of hospitalised patients consistently use corticosteroids, leading to hyperglycaemia in 56%–86% of individuals, regardless of preexisting diabetes.[1] Insulin is the recommended treatment for this hyperglycaemia.[1] Given that sodium-glucose cotransporter 2 inhibitors (SGLT2i) added to insulin therapy typically lower glycaemia and reduce insulin requirements in patients with diabetes,[2,3] we hypothesised that SGLT2i could mitigate hyperglycaemia induced by high-dose corticosteroid therapy in individuals with diabetes. Consequently, we investigated the effects of SGLT2i on hyperglycaemia caused by high-dose intravenous corticosteroid pulse treatment in patients with type 2 diabetes.

2 | METHODS

We retrospectively collected electronic medical records of patients with type 2 diabetes hospitalised at Kyoto University Hospital between April 2014 and March 2022 who received high-dose corticosteroid therapy for facial paralysis or idiopathic sudden sensorineural hearing loss. These patients received intravenous corticosteroid therapy with 200 mg prednisolone sodium succinate daily for 3 days, followed by 100 mg daily for 3 days, and 50 mg daily for another 3 days. Older patients received a half-dose. Preprandial blood glucose levels were measured using point-of-care (POC) testing devices (PocketChem BG, Arkray, Kyoto, Japan). Data on additional insulin doses used during steroid therapy were also collected. The study was approved by Kyoto University Graduate School and Faculty of Medicine Ethics Committee (R2305-3).

Eligible patients were identified from medical records using the medical information unit's sorting system. The criteria were as follows: (1) primary diagnosis of facial paralysis or idiopathic sudden sensorineural hearing loss, (2) comorbid diagnosis of type 2 diabetes, (3) intravenous prednisolone sodium succinate administration and (4) POC capillary (finger-stick) glucose monitoring records measured by healthcare professionals in hospitals. Exclusion criteria included (1) early discharge before the third prednisolone dose and (2) incomplete records of three daily preprandial blood glucose measurements in the hospital.

Demographic and clinical information, including medications, anthropometric data, and HbA1c and preprandial blood glucose levels, were systematically collected from medical records. HbA1c levels

were measured before or shortly after admission. The impact of SGLT2i on mean preprandial blood glucose levels during the 7-day hospital stay (pre-breakfast, pre-lunch and pre-dinner levels from day 2 to day 8) was assessed using multiple linear regression analyses. The effects on add-on insulin administered during the 8-day hospital stay (days 1 to 8) under high-dose corticosteroid therapy were also analysed. Statistical significance was set at $p < 0.05$. JMP Pro®, version 16.2.0 (SAS Institute Inc., Cary, NC, USA) was used for statistical analyses.

3 | RESULTS

From April 2014 to March 2022, data on 46 patients with type 2 diabetes hospitalised for a 9-day course of high-dose intravenous corticosteroids for facial paralysis or idiopathic sudden sensorineural hearing loss were extracted from electronic medical records. Three were excluded due to early discharge, three for incomplete POC blood glucose monitoring, and one for 15 repeated hypoglycaemic episodes, leaving 39 patients for analysis (Figure S1). The mean age was 63.5 years with a standard deviation of 11.7 years, BMI was 26.0 ± 4.4 kg/m^2, HbA1c was 7.4% ± 1.7% (57 mmol/mol), preprandial blood glucose level during prednisolone therapy was 189.6 ± 52.2 mg/dL, and the total additional insulin dose required was 62.8 ± 60.9 units per hospital stay. The concurrent use of medications and patient characteristics are shown in Table 1, stratified by SGLT2 inhibitor use (Table 1).

From potential confounders—age, sex, BMI, HbA1c and prednisolone dose—only HbA1c and age were significant determinants of preprandial blood glucose levels by stepwise regression. For the add-on insulin required for glycaemic control during corticosteroid therapy, HbA1c and pre-therapy insulin dose emerged as significant determinants from the same set of confounders. HbA1c and age were used to adjust the regression model of preprandial blood glucose levels, while HbA1c and pre-therapy insulin dose were used in the regression analysis of insulin dosage.

In contrast to other medications, concurrent SGLT2i use significantly influenced lower mean preprandial blood glucose levels compared with non-use after adjusting for HbA1c and age ($B = -31.8$, $p = 0.048$) (Figure 1). Other medications, including DPP4i ($B = 5.9$, $p = 0.632$), metformin ($B = -17.1$, $p = 0.170$), sulfonylureas ($B = 20.0$, $p = 0.187$), α-glucosidase inhibitors ($B = -18.2$, $p = 0.325$) and meglitinides ($B = -21.0$, $p = 0.316$), did not show a significant influence on preprandial blood glucose levels. Although not statistically significant, concurrent SGLT2i use tended to reduce the additional insulin dose needed to manage glycaemia during corticosteroid therapy after adjusting for HbA1c and pre-corticosteroid insulin doses ($B = -34.8$, $p = 0.060$), a trend not observed with other hypoglycaemic medications, including DPP4i ($B = 8.6$, $p = 0.538$), metformin ($B = -15.4$, $p = 0.282$), sulfonylureas ($B = 6.3$, $p = 0.720$), α-glucosidase inhibitors ($B = -23.9$, $p = 0.257$) and meglitinides ($B = -22.9$, $p = 0.334$). (Figure S2). No adverse events, such as ketosis or urinary tract infection, were reported.

TABLE 1 Characteristics of patients.

	SGLT2i user	SGLT2i no-user	*p* value
Age (years)	61.9 ± 11.3	63.9 ± 11.9	0.486
Male/female (*n*)	5/2	18/14	0.678
Weight (kg)	73.4 ± 16.8	66.5 ± 16.3	0.213
BMI (kg/m^2)	27.2 ± 4.3	25.8 ± 4.5	0.306
HbA1c (NGSP) (%)	8.3 ± 2.8	7.3 ± 1.3	0.486
HbA1c (IFCC) (mmol/mol)	68 ± 31	56 ± 14	—
Half-dose prednisolone (*n*)	1 (14.3)	15 (46.9)	0.206
Concurrent medication			
SGLT2 inhibitors (yes, %)	7 (100)	0	
Insulin (yes, %)	7 (100)	30 (93.8)	1.000
DPP4 inhibitors (yes, %)	5 (71.4)	14 (43.8)	0.235
Metformin (yes, %)	4 (57.1)	11 (34.4)	0.396
Sulfonylurea (yes, %)	1 (14.3)	7 (21.9)	1.000
α-Glucosidase inhibitors (yes, %)	3 (42.9)	3 (9.4)	0.059
Meglitinides (yes, %)	2 (28.6)	2 (6.3)	0.141
GLP-1 RAs (yes, %)	0 (0)	2 (6.3)	1.000
Pioglitazone (yes, %)	0 (0)	1 (3.1)	1.000
Mean preprandial glucose (mg/dL)	182.4 ± 42.3	191.2 ± 54.6	0.714
Add-on insulin doses per hospital stay (units)	62.4 ± 45.8	62.9 ± 64.3	0.855

Note: Data are shown as mean ± SD/number (%). *p* Values are from Wilcoxon rank-sum test and Fisher's exact test.

Abbreviations: BMI, body mass index; GLP-1 RAs, glucagon-like peptide-1 receptor agonists; HbA1c (NGSP), haemoglobin A1c (National Glycohemoglobin Standardization Program).

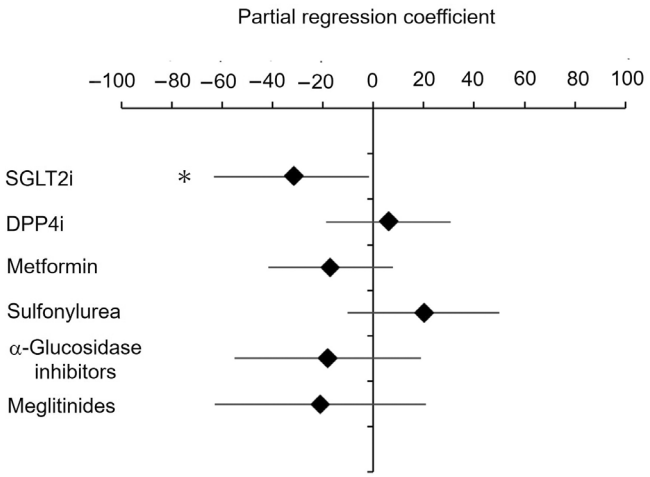

FIGURE 1 Impact of concurrent diabetes medication on steroid-induced hyperglycaemia. The partial regression coefficients of each medication after adjusting for HbA1c and age in the multiple regression analyses for mean preprandial blood glucose levels are indicated by ◆. Error bars indicate 95% confidence interval. A *p* value of <0.05 is presented as *. SGLT2i, sodium-glucose cotransporter 2 inhibitors.

4 | CONCLUSIONS

SGLT2i was the only medication, besides insulin, significantly linked to decreased hyperglycaemia during corticosteroid therapy, requiring a relatively low add-on insulin dose in this observational study. This result is likely due to an insulin-independent effect on the renal glucose threshold. SGLT2i is known to decrease glycaemic excursions,[4,5] and this effect is more pronounced than that of metformin or gliclazide.[6,7] Steroid-induced glucose excursions may be effectively targeted by SGLT2i.

Steroid-induced hyperglycaemia has a poor prognosis.[8] In hospitals, over half of patients on high-dose steroids develop hyperglycaemia,[9] typically managed with insulin injections. Optimal corticosteroid regimens for facial paralysis have been established,[10,11] and systemic corticosteroid therapy for idiopathic sudden sensorineural hearing loss is common in Japan and optional in America.[12,13] Blood glucose increases and insulin dose requirements vary among patients; therefore, insulin adjustments are based on the anticipated dose and duration of glucocorticoid treatment and subsequent glycaemia levels.[1] Daily insulin adjustments require careful management to avoid hypo- or hyperglycaemia.

Glucocorticoids act as counter-regulatory hormones to insulin. Elevated glucocorticoid levels combined with dehydration predispose individuals to ketosis.[14] While no patients in this study showed ketosis symptoms, the risk associated with SGLT2i use under high-dose corticosteroid therapy remains. In hospitalised patients, dehydration can be managed by monitoring and treatment. Patients with facial paralysis or idiopathic sudden sensorineural hearing loss typically maintain good general health, presenting no clear contraindications for SGLT2i.

Individuals with diabetes treated with SGLT2i exhibit reduced hyperglycaemia during high-dose steroid therapy. The potential benefits of continuing SGLT2i in the setting of steroid administration should not be overlooked. However, limitations include the observational design, small sample size, few patients using GLP-1 receptor agonists, and none using GIP/GLP-1 receptor agonist or imeglimin. Further research is needed to confirm the benefits of SGLT2i in patients with diabetes hospitalised for high-dose corticosteroid therapy.

AUTHOR CONTRIBUTIONS

KI conceived the research concept. KI, FMU and YK designed the study. KI and FMU collected data. KI, FMU, YK, DY, NI, KO and YN analysed and interpreted the data. KI wrote the manuscript. All authors reviewed the manuscript. KI had full access to all data and ensured data integrity and accuracy of the analysis.

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CONFLICT OF INTEREST STATEMENT

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PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.16221.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

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REFERENCES

1. Committee ADAPP. 16. Diabetes care in the hospital: standards of care in diabetes-2024. *Diabetes Care*. 2024;47(Suppl 1):S295-S306.

2. Biester T, Muller I, von dem Berge T, et al. Add-on therapy with dapagliflozin under full closed loop control improves time in range in adolescents and young adults with type 1 diabetes: the DAPADream study. *Diabetes Obes Metab*. 2021;23(2):599-608.
3. Giugliano D, Longo M, Caruso P, et al. Feasibility of simplification from a basal-bolus insulin regimen to a fixed-ratio formulation of basal insulin plus a GLP-1RA or to basal insulin plus an SGLT2 inhibitor: BEYOND, a randomized, pragmatic trial. *Diabetes Care*. 2021;44(6):1353-1360.
4. Li M, Liu Z, Yang X, et al. The effect of sodium-glucose cotransporter 2 inhibitors as an adjunct to insulin in patients with type 1 diabetes assessed by continuous glucose monitoring: a systematic review and meta-analysis. *J Diabetes Complications*. 2023;37(12):108632.
5. Matsumura M, Nakatani Y, Tanka S, et al. Efficacy of additional Canagliflozin administration to type 2 diabetes patients receiving insulin therapy: examination of diurnal glycemic patterns using continuous glucose monitoring (CGM). *Diabetes Ther*. 2017;8(4):821-827.
6. Færch K, Blond MB, Bruhn L, et al. The effects of dapagliflozin, metformin or exercise on glycaemic variability in overweight or obese individuals with prediabetes (the PRE-D trial): a multi-arm, randomised, controlled trial. *Diabetologia*. 2021;64(1):42-55.
7. Vianna AGD, Lacerda CS, Pechmann LM, et al. Improved glycaemic variability and time in range with dapagliflozin versus gliclazide modified release among adults with type 2 diabetes, evaluated by continuous glucose monitoring: a 12-week randomized controlled trial. *Diabetes Obes Metab*. 2020;22(4):501-511.
8. Delfs N, Struja T, Gafner S, et al. Outcomes of hospitalized patients with glucocorticoid-induced hyperglycemia-a retrospective analysis. *J Clin Med*. 2020;9(12):4079.
9. Fong AC, Cheung NW. The high incidence of steroid-induced hyperglycaemia in hospital. *Diabetes Res Clin Pract*. 2013;99(3):277-280.
10. Madhok VB, Gagyor I, Daly F, et al. Corticosteroids for Bell's palsy (idiopathic facial paralysis). *Cochrane Database Syst Rev*. 2016;7(7):CD001942.
11. Gupta KK, Balai E, Tang HT, Ahmed AA, Doshi JR. Comparing the use of high-dose to standard-dose corticosteroids for the treatment of Bell's palsy in adults-a systematic review and meta-analysis. *Otol Neurotol*. 2023;44(4):310-316.
12. Kitoh R, Nishio SY, Usami SI. Treatment algorithm for idiopathic sudden sensorineural hearing loss based on epidemiologic surveys of a large Japanese cohort. *Acta Otolaryngol*. 2020;140(1):32-39.
13. Chandrasekhar SS, Tsai Do BS, Schwartz SR, et al. Clinical practice guideline: sudden hearing loss (update). *Otolaryngol Head Neck Surg*. 2019;161(1_suppl):S1-S45.
14. Perry RJ, Rabin-Court A, Song JD, et al. Dehydration and insulinopenia are necessary and sufficient for euglycemic ketoacidosis in SGLT2 inhibitor-treated rats. *Nat Commun*. 2019;10(1):548.

SUPPORTING INFORMATION

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

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