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ORIGINAL RESEARCH

Blood glucose control in acute stroke patients under total energy restriction with different carbohydrate intake and SGLT2 inhibitors availability: a retrospective cohort study

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Abstract

Hyperglycemia in acute stroke patients worsens neurological outcomes. However, effective and safe management during the acute stage has not been established. Therefore, we aimed to compare the effect of medications and nutrition therapy on blood glucose control in three cohorts with different carbohydrate content and availability of sodium-glucose cotransporter 2 inhibitors (SGLT2is) to identify the current optimal treatment for acute-stage hyperglycemia. We retrospectively studied patients with acute stroke admitted to our hospital between 2011 and 2019. We divided the study period into three periods as follows: traditional (Td, 2011–2013), transition (Ts, 2013–2014), and novel (N, 2014–2019). To evaluate glucose-lowering efficacy and safety, we included conscious patients with glycated hemoglobin A1c $\geq$6.5%, blood glucose levels $\geq$11.1 mmol/L, normal renal function at admission, oral diet and medications, and fasting blood glucose (FBG) test on day 7. We performed total energy restriction (TER) in each period with different carbohydrate contents: 60% in Td, 40% in Ts, and N. The attending physicians chose glucose-lowering medications. SGLT2is were available in the N period only. Our target FBG was $<$7 mmol/L by day 7. The 26, 22 and 36 patients were enrolled in the Td, Ts and N periods. The blood glucose levels significantly decreased by day 7 in all periods. The target FBG was achieved in 30.8% of Td patients, 31.8% of Ts patients, and 72.2% of N patients. The N period had the highest population of achieving the target FBG. The 40%-carbohydrate diet based on TER plus SGLT2is was the most effective way to lower blood glucose levels. The N period had the highest population of positive urine ketones. However, no symptomatic ketoacidosis occurred. A 40%-carbohydrate diet based on TER combined with SGLT2is might be a potentially effective and safe treatment for hyperglycemia in acute stroke-conscious patients.

Keywords

Carbohydrate; Diabetes; Energy restriction, Hyperglycemia; SGLT2; Stroke

1. Introduction

Hyperglycemia at the onset of stroke requires treatment because it worsens functional outcomes [1, 2]. Therefore, glucose-lowering treatment is started immediately after admission during the acute stroke phase to improve neurological outcomes. However, intensive insulin treatment may induce severe hypoglycemia [3], and safe and effective therapies for poststroke hyperglycemia have not been established yet.

In the non-acute phase, the first-line glucose-lowering treatment for type 2 diabetes mellitus (T2DM) is meal planning, weight loss, and exercise. In Japan, total energy restriction (TER) is the standard medical nutrition therapy for T2DM to control diet volume and reduce body weight. Therefore, TER is usually performed during the acute stroke stage in Japan, and total energy intake is determined for each patient based on their target body weight (TBW), which may vary depending on the patient's age, body height, and disease condition [4]. In contrast to some Western countries that recommend low-carbohydrate (carb) diets for T2DM [5], a high (60%) carb diet based on TER is standard for conscious patients with T2DM during hospitalization in Japan [4].

Medications for T2DM are essential in the acute phase as well as in the non-acute phase. They help with glucose-lowering management and prevention of cerebrovascular diseases. However, the choice and dose of medications may depend on the type and amount of dietary intake. In patients with severe hyperglycemia, agents with a robust hypoglycemic effect, such as insulin or sulfonylurea (SU), are usually ad-

ministered; however, these agents may cause hypoglycemia if the dietary carbohydrate intake is insufficient or variable. Therefore, an effective and safe pharmacological treatment that can be adjusted to dietary therapy has not been established in the acute phase [3]. In the non-acute stage, some clinical trials of intensive glucose-lowering management in patients with T2DM have failed to reduce cardiovascular events [6–9], probably because of hypoglycemic adverse effects. Non-strong oral medication, for example, pioglitazone, lowers the risk of recurrent major adverse cardiovascular events. However, this drug has been associated with an increased risk of heart failure and bladder cancer [10–12] and is not widely used. On the other hand, recent studies support sodium-glucose cotransporter 2 inhibitors (SGLT2is) as effective drugs for improving cardiovascular morbidity and mortality in patients with T2DM [13–17]. Therefore, the Canadian Stroke Best Practice Recommendations for the Secondary Prevention of Stroke show that SGLT2is should be considered in patients with stroke and T2DM who do not achieve glycemic targets after receiving standard oral antihyperglycemic medications (evidence level B) [13, 14].

Therefore, SGLT2is are promising oral medications for hyperglycemia during the acute phase and secondary prevention after discharge. Indeed, a few studies have reported on the effectiveness and safety of SGLT2is in emergency medicine, showing that SGLT2is can lower glucose levels without increasing the risk of hypoglycemia or ketoacidosis. Although SGLT2is have a diuretic action that can lead to dehydration as an adverse effect [18, 19], this can be prevented by adequate fluid intake and monitoring of hematocrit and albumin levels. Moreover, although SGLT2is have been considered less effective in lowering the blood glucose (BG) levels in elderly T2DM patients with renal disease [20], recent studies have shown that SGLT2is can still provide cardiovascular and renal benefits in this population [14]. Therefore, SGLT2i use is recommended in patients with T2DM who have an estimated glomerular filtration rate (eGFR) of 30 to $\leq$60 mL/min/1.73 m^2 body surface area (BSA) [14] unless they have contraindications or intolerance.

Reducing overall carb intake for individuals with T2DM improves hyperglycemia (level of evidence II, grade B recommendation) [5, 21, 22]. Therefore, a moderate- or low-carb diet probably lowers the BG levels more effectively than a high-carb diet in acute stroke patients with hyperglycemia. Furthermore, a moderate-carb diet combined with SGLT2is has been reported for glucose-lowering management in the acute phase [23].

However, during the acute stroke stage, the glucose-lowering efficacy of the TER diet, low-carb diet based on TER, or low-carb diet based on TER plus SGLT2is for hyperglycemia has not yet been well known. Therefore, in this retrospective cohort study, we aimed to compare the glucose-lowering efficacy and safety of medical nutrition treatments for hyperglycemia in three different cohorts of patients.

2. Materials and methods

2.1 Patients

For this retrospective study, we included patients with acute stroke who met the following criteria: (1) were admitted within 24 h of stroke onset between January 2011 and March 2019; (2) had a BG level $\geq$11.1 mmol/L (200 mg/dL), glycated hemoglobin A1c (HbA1c) level $\geq$6.5%, and an eGFR $\geq$60 mL/min/1.73 m^2 at admission; (3) underwent a fasting BG (FBG) test on day 7; (4) were conscious, and received oral diet and oral drugs during hospitalization; and (5) had not undergone insulin therapy before stroke onset. Our study included patients with normal renal function because SGLT2is should only be started in patients with an eGFR $\geq$60 mL/min/1.73 m^2, according to the 2014 package inserts and recommendations [20]. T2DM was diagnosed by a history of T2DM or a BG level $\geq$11.1 mmol/L combined with HbA1c $\geq$6.5% at admission. We excluded patients fed through a nasogastric tube because feeding through a nasogastric tube was not considered oral ingestion, and we excluded patients with an onset-to-door time $>$24 h because we planned to investigate the effectiveness of treatments in patients with hyperglycemia at the onset of acute stroke.

2.2 Baseline nutrition therapy

We performed TER as Japan's baseline nutrition therapy for T2DM [4]. The total energy intake was determined during hospitalization for each patient. We determined the standard body weight (BW) in Japanese as the TBW [24], which was calculated as follows [4]:

TBW = body height $\times$ body height $\times$ 22 kg/m^2

The target total energy (TTE) for the TER was calculated as follows [4]:

TTE = TBW $\times$ 25 kcal/kg

A TER diet for hospitalization was determined (Table 1).

TABLE 1. Total energy-restriction diet for hospitalization.

TTE	A TER diet
1000 kcal $\leq$ TTE $<$ 1200 kcal	1000 kcal/day
1200 kcal $\leq$ TTE $<$ 1400 kcal	1200 kcal/day
1400 kcal $\leq$ TTE $<$ 1600 kcal	1400 kcal/day
1600 kcal $\leq$ TTE $<$ 1800 kcal	1600 kcal/day
1800 kcal $\leq$ TTE $<$ 2000 kcal	1800 kcal/day

TER, total energy restriction; TTE, target total energy.

2.3 Carbohydrate management

The 60%-carb diet based on TER is the standard during hospitalization in Japan. In October 2013, the 40%-carb diet became available in our institution, and we started providing patients with the 40%-carb diet based on TER for hyperglycemia (Table 2).

2.4 Pharmacotherapy

In each period, the attending physicians chose glucose-lowering agents. A long-acting insulin analog (LIA) was

TABLE 2. Nutrition treatment period, carbohydrate content, and SGLT2i treatment.

Periods	Month Year	TER	carb	SGLT2i treatment	Traditional medications
Traditional	Jan 2011–Sep 2013	TER	60%	No	Use
Transition	Oct 2013–Sep 2014	TER	40%	No	Use
Novel	Sep 2014–Mar 2019	TER	40%	Yes	Use

Carb, carbohydrate content; Jan, January; Mar, March; Novel, a 40%-carbohydrate diet based on TER with SGLT2i in the novel period; Oct, October; Sep, September; SGLT2i, sodium-glucose cotransporter 2 inhibitors; TER, total energy restriction; Traditional, a 60%-carbohydrate diet based on TER in the traditional period; Transition, a 40%-carbohydrate diet based on TER in the transition period.

administered when the FBG level on the day after admission was >13.8 mmol/L (250 mg/dL). The initial LIA dose was two units, and the drug was discontinued when the FBG level had decreased to <5.6 mmol/L (100 mg/dL). The attending physicians determined increases or decreases in the LIA dosage. Using a portable glucose meter, they checked the BG levels before breakfast, lunch, dinner, and lights-out time. The day after admission, oral medications were started when a portable glucose meter showed an FBG level ≥7.0 mmol/L (126 mg/dL).

SGLT2is were approved in April 2014 in Japan, and we started to use SGLT2is in October 2014 in patients with normal renal function, according to the 2014 package inserts and recommendations [20]. Adverse effects of dehydration due to osmotic diuresis have been reported for SGLT2is. Therefore, we are afraid that a high-carb diet induces higher BG levels and higher osmotic diuresis in diabetes patients than a low-carb diet, and SGLT2is are always used not with the 60%-carb diet but with the 40%-carb diet. Moreover, when the 40%-carb diet based on TER and medications other than SGLT2is lowered the FBG level to <11.1 mmol/L (200 mg/dL) on day 3 after admission, SGLT2is were initiated.

2.5 Traditional, transition and novel treatment periods (Table 2)

We divided our analysis into three treatment periods based on the carb content of the diet and SGLT2i treatment, as shown in Table 1. In each period, we performed total energy restriction (TER) with different carbohydrate (carb) contents: 60% in the traditional (Td) treatment period and 40% in transition (Ts) and novel (N) treatment periods. Glucose-lowering agents were delegated to the attending physicians. SGLT2is were approved in April 2014 in Japan, and we started to use them in the N period. In each period, the attending physicians intended to perform the best medical nutrition treatment for patients with hyperglycemia.

The Td period was from January 2011 to September 2013, the Ts period from October 2013 to September 2014, and the N period from October 2014 to March 2019. Patients were treated with the 60%-carb diet based on TER and traditional medications in the Td period, with the 40%-carb diet based on TER and conventional medicines in the Ts period, and with the 40%-carb diet based on TER and SGLT2is in the N period. Patients ate three meals per day. The total energy intake was divided equivalently in the Td period; however, the energy intake for breakfast, lunch, and dinner was in the ratio of 5:5:4 in the Ts and N periods. The carb component (quantity) was divided equivalently in the Td period; however, the carb component for breakfast, lunch, and dinner was in the ratio of 5:5:4 in the Ts and N periods.

2.6 Evaluation

We evaluated anthropometric variables, such as the BW, body height, body mass index, TTE, daily carb intake, serum lipid level, BG level at admission, FBG level on days 3 and 7 after admission, achievement of the target FBG on day 7, HbA1c at admission, hematocrit (Hct) level at admission and on day 7, urine glucose (U-glucose) and urine ketones (U-ketone) at admission and on day 7, use of glucose-lowering agents (*i.e.*, sulfonylurea (SU)) during hospitalization, and use of basal insulin therapy on day 7. If the U-ketone score was high, the diabetic ketoacidosis (DKA) signs and symptoms were checked. In addition, the Hct levels were measured to determine dehydration during hospitalization. Polyuria, polydipsia, dyspnea, nausea and vomiting, abdominal pain, and weakness comprised probable DKA signs and symptoms [25, 26].

A day-7 FBG test was defined as an FBG test performed on days 6, 7 or 8 after admission. The target FBG level on day 7 was <7.0 mmol/L (126 mg/dL). We defined a day-7 high dose of LIA as ≥10 units. A urine strip test was performed to check for glucose or ketones. The test scores ranged from 0 to 4 points. A value of zero indicates no glucose or ketones in the urine. We defined the high Hct level on day 7 as >50 in males or >45 in females. In addition, we determined the high U-glucose score on day 7 as 4 points and the high U-ketone score on day 7 as 3 or 4 points.

2.7 Targets

An efficacy endpoint was achieving the day-7 target FBG level. Safety endpoints were evaluated as follows: no use of day-7 SU drugs or LIA; day-7 low LIA dose; day-7 low Hct level; day-7 low U-glucose score; or day-7 low U-ketone score.

2.8 Statistical analysis

The chi-square test was used to compare categorical variables. When the cell count was below 5, Fisher's exact test was performed. When this test indicated a significant difference among the three periods, the Bonferroni correction was used to compare all possible pairs of variables among the three periods. Non-normally distributed continuous variables were expressed

as medians and interquartile ranges. The Wilcoxon rank-sum test compared continuous variables between the two groups or among the three groups. When the Wilcoxon rank-sum test indicated a significant difference in continuous variables among the three groups, Dunn's test was used to compare all possible pairs of continuous variables among the three groups. The Wilcoxon signed-rank test compared continuous variables between the paired groups. Statistical significance was set at $p < 0.05$. We used JMP software (version 17.2; SAS Institute, Cary, NC, USA) for all statistical analyses. One author (TM) had full access to all study data and took responsibility for its integrity and analysis.

3. Results

Of 5724 patients with acute stroke, 84 met our inclusion and exclusion criteria for analysis. We enrolled 26 patients in the Td period, 22 in the Ts period, and 36 in the N period (Fig. 1, Table 2). Patient characteristics at admission in each period were summarized in Table 3. Diabetic medications before admission were summarized in **Supplementary Tables 1 and 2**. About 40% of patients in each period received monotherapy or combination therapy with diabetic medications before acute stroke. None of the patients were treated with SGLT2is before admission. There were no significant differences in age, sex, stroke severity, and pre-stroke diabetes medications.

Three types of SGLT2is were used in the N period (Table 4). The median daily carb intake was 195 g in the Td period, whereas 140 g was in the Ts and N periods (Table 5). In each period, the attending physicians chose glucose-lowering agents (**Supplementary Tables 3 and 4**), and the BG levels significantly decreased from admission to day 3 and from day 3 to day 7 (Fig. 2, **Supplementary Table 5**). The day-7 FBG level was the lowest in the N period ($p = 0.0003$), and more patients achieved the day-7 target FBG levels in the N period than in the Td or Ts periods ($p = 0.0008$) (Table 5, Fig. 2, **Supplementary Tables 6 and 7**). SU was used the most frequently in the Td period, whereas no SU in the N period ($p < 0.0001$) (Table 5). There were no differences in the frequency of dipeptidyl peptidase 4 inhibitor (DPP4) use among three periods; however, there were differences in the frequency of biguanide or SU use between the Td and Ts periods (**Supplementary Tables 4 and 8**). There were no differences in the frequency of LIA use on day 7 among the three periods (Table 5, **Supplementary Table 9**); however, the median LIA dose of 15 units in the Td period was high, compared to six LIA units in the N period (**Supplementary Table 10**).

The day-7 U-glucose and U-ketone scores were the highest in the N period (Table 5, **Supplementary Tables 11 and 12**). Fortunately, no patients with day-7 high U-ketone scores presented signs or symptoms of DKA. The Hct levels in each period decreased from admission to day 7 (Table 5, **Supplementary Table 13**, and no symptomatic dehydration occurred in any patients.

4. Discussion

Our findings suggest that the TER diet can lower BG levels during the acute stroke stage, and especially the 40%-carb diet

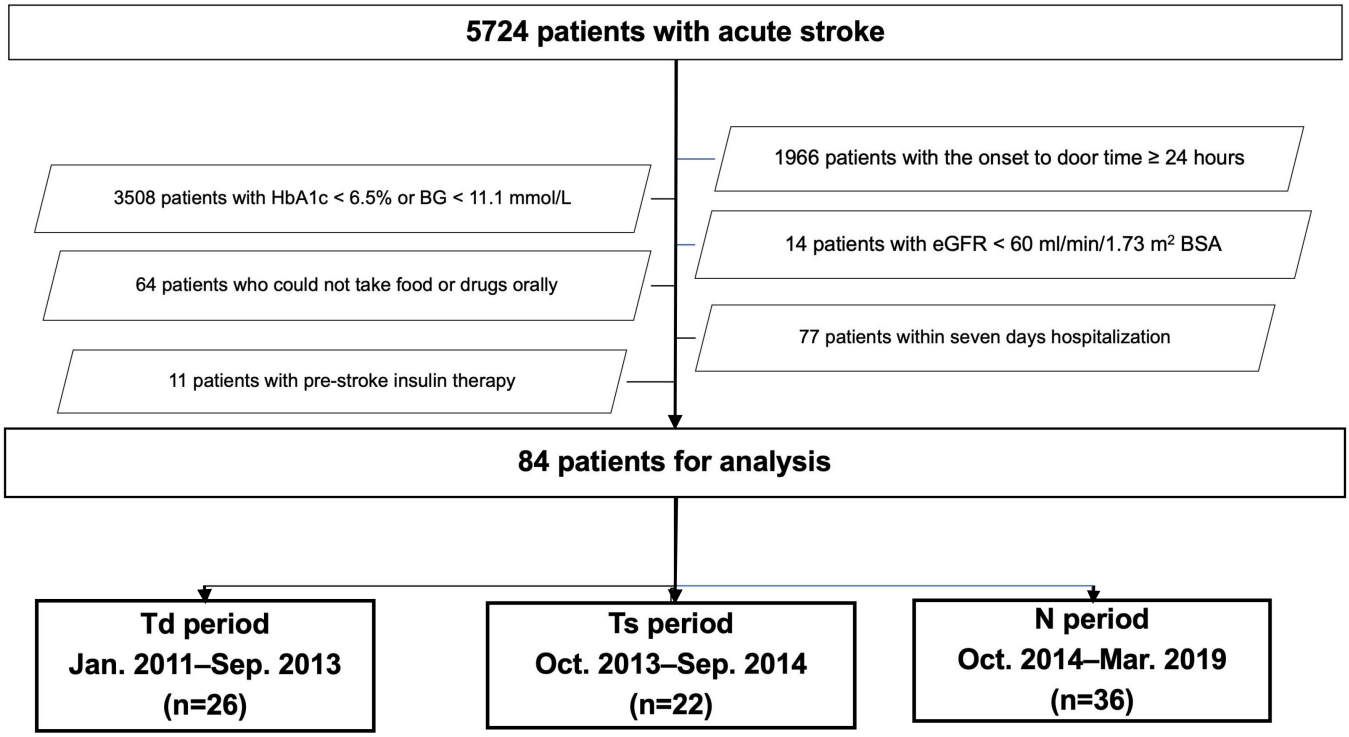

FIGURE 1. Flow chart of patient selection for analysis. BG, blood glucose; BSA, body surface area; N, 40%-carb diet based on TER with SGLT2i in the novel period; Ts, 40%-carb diet based on TER in the transition period; Td, 60%-carb diet based on TER in the traditional period; carb, carbohydrate; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; n, number; SGLT2i, sodium-glucose cotransporter 2 inhibitors; TER, total energy restriction.

TABLE 3. Comparison of baseline patient characteristics at admission.

Variables	Periods		
	Novel n = 36	Transition n = 22	Traditional n = 26
Ischemic, n (%)	34 (94.4%)	18 (81.8%)	23 (88.5%)
Male sex, n (%)	34 (94.4%)	11 (50.0%)	19 (73.1%)
Age, y	68 (62.3–76.5)	62 (55.5–71.3)	70 (62.0–82.3)
BMI, kg/m^2	24.3 (22.3–27.4)	25.1 (22.4–29.4)	24.1 (21.0–25.8)
BH, m	1.64 (1.60–1.68)	1.60 (1.56–1.69)	1.64 (1.56–1.70)
BW, kg	64 (59.3–77.3)	65 (57.5–83.5)	62 (60.3–70.0)
Alb, g/L	41.5 (39.0–43.8)	41.0 (37.8–45.0)	42.0 (40.0–44.0)
Cre, mol/L	62.8 (54.6–72.5)	50.8 (45.8–61.7)	68.1 (48.4–75.1)
eGFR, mL/min/1.73 m^2	74.2 (67.2–91.0)	89.8 (76.4–101.2)	75.4 (66.7–82.2)
BG, mmol/L	14.4 (12.2–18.6)	14.6 (12.7–16.9)	14.2 (13.1–16.3)
HbA1c, %	9.5 (7.8–11.5)	8.9 (7.9–10.7)	8.3 (7.6–10.7)
TC, mmol/L	5.47 (4.80–6.44)	5.82 (4.89–6.47)	5.35 (4.65–6.03)
LDL-C, mmol/L	3.41 (2.72–4.03)	3.03 (2.44–3.75)	2.88 (2.45–3.84)
HDL-C, mmol/L	1.31 (1.07–1.71)	1.39 (1.16–1.65)	1.40 (1.11–1.80)
TG, mmol/L	1.76 (1.02–2.22)	1.96 (1.22–3.52)	1.44 (1.05–2.03)
CRP, g/L	1900 (525–4650)	800 (400–1800)	1200 (400–11,600)
NIHSS at admission	2 (1.0–3.0)	3 (1.8–4.5)	4 (2.0–7.0)
NIHSS at discharge	1 (0.3–2.0)	2 (1.0–5.3)	1 (0.5–5.0)
Hospitalization, days	8 (8–9)	8 (8–9)	8 (7–9)
Discharge to home, n (%)	18 (50.0%)	7 (31.8%)	8 (30.8%)

All values except the categorical data are presented as median (interquartile ranges). Alb, albumin; BG, blood glucose level; BH, body height; BMI; body mass index; BSA, body surface area; BW, body weight; Cre, creatinine; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin A1c; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; n, number; NGSP, National Glycohemoglobin Standardization Program; NIHSS, National Institutes of Health Stroke Scale score; Novel, a 40%-carbohydrate diet based on TER with SGLT2i in the novel period; SGLT2, sodium-glucose cotransporter 2 inhibitors; TC, total cholesterol; TG, triglycerides; Traditional, a 60%-carbohydrate diet based on TER in the traditional period; Transition, a 40%-carbohydrate diet based on TER in the transition period.

TABLE 4. SGLT2i used in the novel treatment period.

SGLT2i	n
Luseogliflozin hydrate 2.5 mg per day	17
Dapagliflozin propylene glycolate hydrate 5 mg per day	14
Canagliflozin hydrate 100 mg per day	5
Total	36

n, number; SGLT2i, sodium-glucose cotransporter 2 inhibitors.

based on TER plus SGLT2is may lower BG levels without SU or high-dose LIA.

The 60%-carb diet based on TER combined with traditional medications other than SGLT2is is the current standard acute-phase medical nutrition treatment in Japanese institutions. However, the 40%-carb diet based on TER, SGLT2i use, or the 40%-carb diet based on TER combined with SGLT2is may develop as the acute-phase medical nutrition treatment in the future. We used SGLT2is in patients with normal renal function, according to the 2014 recommendations. However, the American Diabetes Association and the European Association for the Study of Diabetes, updated in 2020, recommend SGLT2is in patients with eGFR of 30 to <60 mL/min/1.73 m^2 [14].

Although pioglitazone aids in stroke prevention in patients with positive insulin resistance [13, 27], pioglitazone was not used before admission and during hospitalization in any of our patients, probably because pioglitazone increases the risk of bladder cancer [12]. In the empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes study, empagliflozin reduced the mortality rates from cardiovascular causes compared with a placebo [17]. In the canagliflozin cardiovascular assessment study program, canagliflozin reduced cardiovascular events [28]. However, dapagliflozin did not reduce major adverse cardiovascular events in the DECLARE-TIME 58 study [29]. In the comparative effectiveness of cardiovascular outcomes in new users of sodium-glucose cotransporter-2 inhibitors study, SGLT2is, including

TABLE 5. Comparison of diet, glucose, hematocrit, urine and drugs among the three groups.

Variables	Periods			*p*-value
	N n = 36	Ts n = 22	Td n = 26	
Energy-restricted diet, kcal	1400 (1250–1550)	1400 (1200–1400)	1300 (1200–1400)	0.1129
Carb restriction, g	140 (125–155)	140 (120–140)	195 (180–210)*	<0.0001
BG adm, mmol/L	14.4 (12.2–18.6)	14.6 (12.7–16.9)	14.2 (13.1–16.3)	0.9432
Day-3 FBG, mmol/L	9.0 (7.6–10.7)	9.7 (8.5–10.9)	9.9 (7.5–11.2)	0.4449
Day-7 FBG, mmol/L	6.4 (5.8–7.0)*	8.2 (6.8–10.3)	8.0 (6.4–8.7)	0.0003
Day-7 FBG <7.0 mmol/L, n (%)	26 (72.2%)*	7 (31.8%)	8 (30.8%)	0.0008
Hct at admission, %	43.3 (39.7–45.6)	44.1 (40.5–46.7)	42.4 (40.0–45.1)	0.3841
Day-7 Hct, %	40.5 (38.9–43.1)	41.7 (39.1–45.1)	40.5 (38.0–43.3)	0.4706
Day-7 high Hct, n (%)	1 (2.8%)	2 (9.1%)	0 (0%)	0.1881
U-glu score at admission	3 (1.3–4.0)	4 (2.0–4.0)	3 (0.5–4.0)	0.3951
Day-7 U-glu score	4.0 (4.0–4.0)*	0.3 (0–3.0)	0 (0–1.8)	<0.0001
Day-7 high U-glu score, n (%)	34 (94.4%)*	1 (4.6%)	0 (0%)	<0.0001
U-ketone score at admission	0 (0–0)	0 (0–2)	0 (0–0)	0.0560
Day-7 U-ketone score	2 (0.5–3.0)*	0 (0–0)	0 (0–0)	<0.0001
Day-7 high U-ketone score, n (%)	13 (36.1%)#	2 (9.1%)	1 (3.8%)	0.0084
Day-7 SU use, n (%)	0 (0%)	2 (9.1%)	12 (46.2%)*	<0.0001
Day-7 LIA use, n (%)	7 (19.4%)	4 (18.2%)	5 (19.2%)	0.9926
Day-7 dose of LIA ≥10 units, n (%)	1 (2.8%)	2 (9.1%)	3 (11.5%)	0.6975

*All values except the categorical data are presented as median (interquartile ranges). N, a 40%-carbohydrate diet based on TER with SGLT2i in the novel period; Ts, a 40%-carbohydrate diet based on TER in the transition period; Td, a 60%-carbohydrate diet based on TER in the traditional period; FBG, fasting blood glucose; Hct, hematocrit; LIA, long-acting insulin analog; n, number; p, probability; SGLT2i, sodium-glucose cotransporter 2 inhibitors; U-glu, urine glucose; SU, sulfonylurea; U-ketone, urine ketones. *, statistical significance compared to other diet groups, #, statistical significance compared to the Td period.*

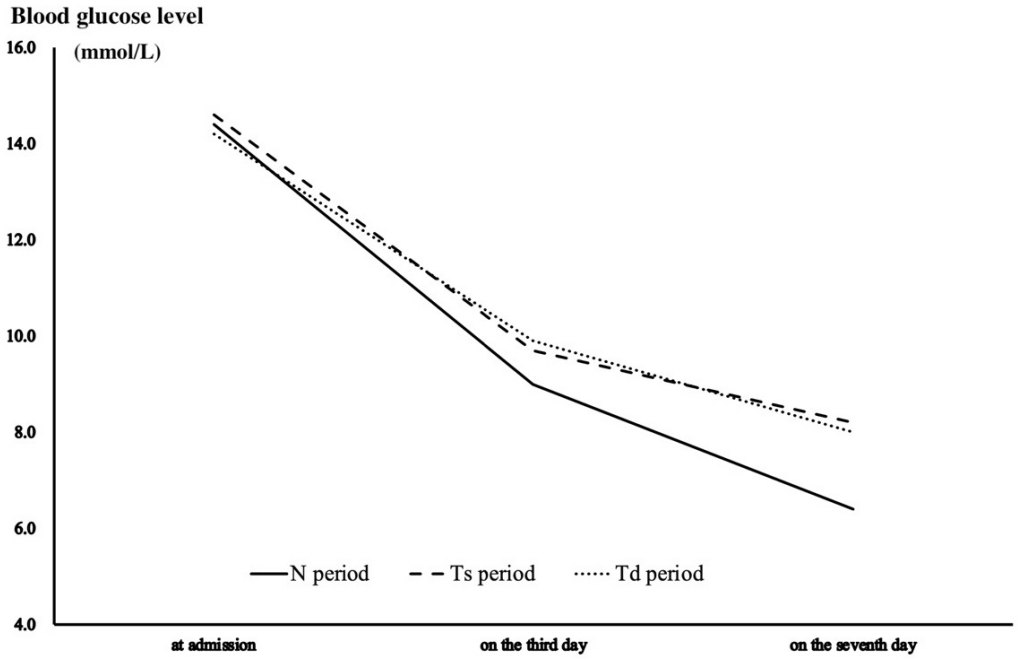

FIGURE 2. Serial changes in blood glucose levels in the three groups. N, 40%-carb diet based on TER with SGLT2i in the novel period; Ts, 40%-carb diet based on TER in the transition period; Td, 60%-carb diet based on TER in the traditional period; carb, carbohydrate; SGLT2i, sodium-glucose cotransporter 2 inhibitors; TER, total energy restriction.

dapagliflozin, empagliflozin, canagliflozin, luseogliflozin, tofogliflozin, or ipragliflozin, were associated with a lower risk of developing cardiovascular events [30]. In the dapagliflozin and prevention of adverse outcomes in heart failure trial, dapagliflozin reduced the risk of worsening heart failure or death from cardiovascular causes [31, 32]. Therefore, the Canadian Stroke Best Practice Recommendations for the Secondary Prevention of Stroke show that SGLT2is should be considered in patients with stroke and T2DM [13].

In addition, the current clinical practice recommendation of the American Diabetes Association recommends SGLT2is as part of the comprehensive cardiovascular risk reduction among patients who have atherosclerotic cardiovascular disease [33]. SGLT2is reduce the risk of worsening heart failure and cardiovascular death in patients with T2DM [33]. SGLT2is have not yet been recommended in emergency medicine [34, 35]; however, glucose-lowering drugs used in the acute phase may often continue to be used after discharge [34, 35]. Therefore, using SGLT2is in the acute phase and at discharge may be helpful for secondary prevention in T2DM patients with cardiovascular disease.

Luseogliflozin, available in Japan, was used in 17 of 36 patients (47.2%) in the present study (Table 4) because luseogliflozin can be used even in patients with renal dysfunction [36, 37].

The 40%-carb diet based on TER combined with SGLT2is was a relatively safe medical nutrition therapy in the N period because it lowered BG levels without the need for SU or a high-dose LIA, which may cause hypoglycemia. On the other hand, the TS period also used the 40%-carb diet based on TER but without SGLT2is. The BG level in the TS period did not decrease as much as that in the N period, but it still required less SU and day-7 LIA units than the Td period, which used the 60%-carb diet based on TER. There were no differences in the day-7 BG levels between the Td and Ts periods, indicating that the 40%-carb diet based on TER may require less SU or LIA to lower BG levels than the 60%-carb diet based on TER (Fig. 2).

In the N period, the BG level decreased promptly in our patients with eGFR $\geq$60 mL/min/1.73 m^2. However, the effects of SGLT2is on stroke may vary according to the level of kidney function [38], and the risk of fatal or nonfatal stroke was low in patients with an eGFR 30 to $<$45 mL/min/1.73 m^2 [39]. Therefore, SGLT2is may not be superior for secondary stroke prevention in patients with eGFR $\geq$60 mL/min/1.73 m^2 compared to those with an eGFR $<$60 mL/min/1.73 m^2. Furthermore, euglycemic DKA has been reported in patients treated with SGLT2is [40]. Consistent with this, in our study, 13 (36.1%) of 36 patients in the N period had U-ketone scores $\geq$3 points on day 7, although they were asymptomatic. Therefore, patients treated with SGLT2is must be conscious and be monitored for signs and symptoms of euglycemic DKA. The BG levels decreased in the Td and Ts periods, indicating that hyperglycemia in both periods was caused by pre-stroke diets with large carbs. Although there were differences in the frequency of biguanide and SU use between the two periods, the TER diet lowered the BG levels in both periods.

A carbohydrate-restricted diet is effective in managing Japanese diabetes outpatients [41]. SGLT2is, combined with a moderate-carb-TER diet, improves hyperglycemia promptly and does not carry a risk of severe hypoglycemia; therefore, it may be the first-line treatment option for hyperglycemia in patients with acute stroke. However, dehydration and DKA must be prevented.

Our study has several limitations. First, our study had a retrospective cohort design, and a small number of patients were analyzed. Therefore, selection bias might have occurred. Patients in three cohorts underwent different pharmacological treatments and nutrition therapy. Future studies should investigate patients with hyperglycemia combined with HbA1c $<$6.5% or eGFR $<$60 mL/min/1.73 m^2. These patients may respond differently to the 40%-carb diet based on TER or SGLT2is. Moreover, our study population is not representative of acute stroke patients with T2DM. Most patients were Japanese. Therefore, the generalizability of the study outcomes to non-Japanese populations is uncertain. Racial differences may exist in the treatment efficacy of the 40%-carb diet based on TER combined with SGLT2is.

Second, inaccurate dietary calories and carbohydrate provision might have introduced information bias. Third, different pharmacological treatments by attending physicians in each period might have affected the endpoints. Additionally, insulin degludec was approved in March 2013, and SGLT2is were approved in April 2014 in Japan. Therefore, the medications that the attending physicians can prescribe differ in each period, and treatment efficacy and safety of three periods cannot be simply compared. Moreover, diuretics influence BG levels because of dehydration. However, we did not investigate the use of diuretics during hospitalization because we only used diuretics for ischemic stroke patients with congestive heart failure or some hemorrhagic stroke patients. Finally, long-term clinical outcomes were not investigated. Thus, a prospective study is needed in the future.

5. Conclusions

The diet based on TER can lower BG levels during the acute stroke stage in conscious patients with normal renal function. The 40%-carb diet may require less SU or high-dose LIA than the 60%-carb diet, and especially the 40%-carb diet based on TER combined with SGLT2is may be the most effective way to lower BG levels without SU or high-dose LIA, suggesting that the 40%-carb diet based on TER combined with SGLT2is could be a promising medical nutrition therapy. However, further prospective studies are needed to confirm our findings and establish the optimal carbohydrate level and medication combination for hyperglycemia in acute stroke patients.

ABBREVIATIONS

BSA, body surface area; carb, carbohydrate; DKA, diabetic ketoacidosis; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; Hct, hematocrit; LIA, long-acting insulin analog; N, novel; SGLT2is, sodium-glucose cotransporter 2 inhibitors; SU, sulfonylurea; TBW, target body weight; T2DM, type 2 diabetes mellitus; TER, total energy restriction; Td, traditional; Ts, transition; TTE, target total energy.

AVAILABILITY OF DATA AND MATERIALS

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

AUTHOR CONTRIBUTIONS

TM—designed the research study; performed the research; analyzed the data; wrote the manuscript. TY, KY and YM—provided help on data collection. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All procedures were performed in accordance with the ethical standards of the institution and the 1964 Declaration of Helsinki. The Tokushukai Group Ethics Committee approved our retrospective study on 09 July 2021 (TGE01737-024). The Tokushukai Group Ethics Committee waived written informed consent, because the enrollment of study participants was based on an opt-out model.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.signavitae.com/mre-signavitae/article/1788086470979796992/attachment/Supplementary%20material.docx.

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