Risk of Hyperglycemia and Hypoglycemia in Patients with Acute Ischemic Stroke Based on Continuous Glucose Monitoring

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Background: In patients with acute ischemic stroke, current guidelines recommend maintaining blood glucose levels in a range of 140-180 mg/dL and closely monitoring to prevent hypoglycemia (<60 mg/dL). We aimed to assess glucose variability by continuous glucose monitoring (CGM) and to demonstrate the risk of acute ischemic stroke patients with glucose levels outside of the glucose management recommendations. *Methods:* Patients with ischemic stroke admitted within 7 days after onset were prospectively enrolled, and their blood glucose levels were monitored every 15 minutes for 72-hour period using the FreeStyle Libre Pro. Multivariate logistic regression analyses were used to analyze potential predictors for hyperglycemic (>180 mg/dL) and hypoglycemic (<60 mg/dL) events. *Results:* A total of 39 acute ischemic stroke patients (mean age 75.9 ± 11.5 years) were enrolled, and CGM was started from 58.6 ± 41.9 hours after stroke onset. CGM showed hypoglycemic events in 19 patients and hyperglycemic events in 21 patients, and the frequencies of hypo- and hyperglycemic events during CGM were 10.1 ± 15.7% and 11.9 ± 22.5%, respectively. Hypoglycemic events were mainly observed in the night-time in patients with normoglycemia at admission. Logistic regression analyses demonstrated significant associations between the blood glucose level at admission and hypo- and hyperglycemic events on CGM. *Conclusions:* This study of CGM found that many stroke patients have blood glucose levels outside the recommended guideline range in the acute phase. Blood glucose level on admission may be used as a predictor for hypo- and hyperglycemic events after admission.

Key Words: Continuous glucose monitoring (CGM)—hypoglycemia—hyperglycemia—acute stroke

Abbreviations: AIS, Acute Ischemic Stroke; BMI, Body Mass Index; CGM, continuous glucose monitoring; CRP, C-reactive protein; DIV, drip infusion; DL, dyslipidemia; DM, diabetes mellitus; DPP-4, dipeptidyl peptidase-4; GLU, blood glucose; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HT, hypertension; LDL, low-density lipoprotein; MRI, magnetic resonance imaging; NGSP, National Glycohemoglobin Standardization Program; NIHSS, National Institute of Health Stroke Scale; mRS, modified Rankin Scale; SD, standard deviation; SU, sulfonyl urea; TG, triglyceride; TOAST, Trial of Org 10172 in Acute Stroke Treatment

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Introduction

Current guidelines[1] recommend that it is reasonable to treat hyperglycemia to achieve blood glucose levels in a range of 140-180 mg/dL and to closely monitor to prevent hypoglycemia (>60 mg/dL) in patients with acute ischemic stroke (AIS). Although a causal relationship has not been elucidated even by a randomized efficacy trial of hyperglycemia treatment in acute stroke (the Glucose Insulin-Stroke Trial−UK),[2] multiple observational studies have consistently found an association between acute stroke hyperglycemia and worse clinical outcomes.[3-6] It is also well known that severe or prolonged hypoglycemia can result in permanent brain damage. To adhere strictly to the guidelines by avoidance of hypoglycemia and hyperglycemia, frequent blood glucose monitoring is needed, but it may result in excessive use of healthcare resources. Glucose monitoring of AIS patients should be individualized based on the risk of abnormal glucose levels outside of the recommendations. Recently, continuous glucose monitoring (CGM) has become available to measure several parameters related to blood glucose variability in AIS patients.[7-10] The aim of the present study was to demonstrate the risk profile of AIS patients who will develop abnormal CGM glucose levels (<60 mg/dL and >180 mg/dL) in order to establish suitable blood glucose monitoring in the management of AIS patients.

Subjects and Methods

Patients (≥20 years old) with AIS admitted within 7 days after onset were prospectively enrolled. Excluded were patients with: (1) pregnancy, (2) hemodialysis, (3) another implanted device such as a pacemaker, (4) serious illness, and (5) upper arm skin disorder. To minimize potential patient selection bias, consecutive potentially eligible patients were invited to participate. There was no protocol obligation for blood glucose monitoring during CGM. Glucose measurements by finger-stick or blood sampling were performed at the physician's discretion during CGM. Attending physicians were blinded to the results of CGM. The study protocol was approved by the St. Marianna University Bioethics Committee (No.4170), and registered with UMIN Clinical Trials Registry (number 000036964). Informed consent to participate was obtained from all patients or their families.

Continuous Glucose Monitoring

After the initial magnetic resonance imaging (MRI) assessment, a small, round sensor (35 mm in diameter), the FreeStyle Libre Pro (Abbott Japan Inc., Tokyo, Japan), was applied on the back of the upper arm. Glucose levels in interstitial fluid are continuously measured through a small (<.4 mm thick, 5 mm long) filament that is inserted just under the skin every 15 minutes. This CGM system does not require finger-stick calibration, but a physiological difference between the interstitial fluid and capillary blood, such as severe dehydration, results in differences in glucose readings. Taking medications, such as ascorbic acid, salicylic acid, and acetaminophen, may result in false glucose readings.[11] CGM was continued for up to 14 days, but the initial 288 glucose values for 72 hours were used for the statistical analyses to exclude physiological differences in the late phase. When patients needed to have an MRI examination while being monitored by the FreeStyle Libre Pro, the glucose monitor was temporarily removed prior to MRI scanning and replaced after the completion of the MRI scanning. Data for 72 hours were obtained for all patients.

In this study, hypoglycemia and hyperglycemia were defined as CGM glucose levels less than 60 mg/dL and gretaer than 180 mg/dL, respectively. The following parameters were calculated using CGM: (1) mean, (2) standard deviation (SD) of glucose levels, (3) frequency (%) of hypoglycemia (<60 mg/dL), and (4) frequency (%) of hyperglycemia (>180 mg/dL). To assess the effects of oral intake, these parameters were also calculated in the daytime (6:00-24:00) and in the night-time (00:01-05:59).[12] Furthermore, nutritional intake type during CGM was categorized into 3 types: (1) drip infusion only (no oral intake), (2) oral intake with drip infusion, and (3) oral intake only.

Clinical Data Collection

On admission, demographic data, including past history, comorbidities, medical treatment before admission, body mass index, and neurological deficit (National Institutes of Health Stroke Scale score)[13] were recorded. The stroke subtype was diagnosed at admission according to the Trial of ORG 10172 in Acute Stroke Treatment classification on the basis of clinical data including neuroimaging.[14]

Regarding comorbidities, hypertension was defined as 2 or more blood pressure measurements of greater than or equal to 140/90 mmHg after the 14th hospital day, or a previous diagnosis of hypertension and use of antihypertensive agents. Dyslipidemia was defined as low-density lipoprotein cholesterol greater than or equal to 140 mg/dL, neutral fat levels greater than or equal to 150 mg/dL, high-density lipoprotein cholesterol less than 40 mg/dL, or use of oral agents. Diabetes mellitus (type 2) was considered present if the patient showed fasting blood glucose levels greater than or equal to 126 mg/dL and hemoglobin A1c greater than or equal to 6.5%, or if treatment for diabetes was being administered. During the CGM, use of insulin or oral agents for diabetes mellitus, oral feeding type, total daily calories, and blood glucose measurements by the pin-prick method, if present, were recorded.

Statistical Analysis

The characteristics of the study subjects are presented as means and SD, unless otherwise indicated. Unpaired Student's t tests were used to compare continuous variables, and χ^2 tests were used for nominal parameters. The

Mann-Whitney test was used for data that were not normally distributed. Multivariate logistic regression analysis was used to analyze potential predictors for hypoglycemia (<60 mg/dL) or hyperglycemia (>180 mg/dL) detected on CGM. The highest quartile of frequencies of hypo- and hyperglycemic events was used as a dependent variable for the logistic regression analysis. These methods may be conservative to demonstrate AIS patients with a risk of hypo- and hyperglycemic events, but CGM glucose values might not always coincide with blood glucose values because of changes in physiological status or medications. The results of a clinical study showed that 40% of the time when the device indicated hypoglycemia (<60 mg/dL), capillary glucose values were actually in the range of 81-160 mg/dL.[10] Thus, the highest quartile method is reasonable to provide clinically relevant risk profiles. A P value < .05 was considered significant (2-tailed). All statistical analyses were performed using SPSS version 25 (IBM SPSS Statistics for Windows; IBM Corp, Armonk, NY).

Results

A total of 39 AIS patients (23 male and 16 female; mean age 75.9 ± 11.5 years) were enrolled from April to November, 2018 (Table 1). CGM was started from 58.6 ± 41.9 hours after stroke onset, and a total of 288 glucose measurements were obtained for 72 hours in all patients. Patients' characteristics are shown in Table 1. The mean body mass index was 21.8 ± 3.7 kg/m^2, and 12 patients (30.8%) had diabetes mellitus. During CGM, there were 10 patients (25.6%) who were treated by insulin or oral hypoglycemic agents. The most common subtype of AIS was large-artery atherosclerosis (14 patients, 35.9%). Numbers with cardioembolism, small-vessel occlusion, stroke of other determined etiology, and stroke of undetermined etiology were 7, 7, 5, and 6, respectively. The mean National Institutes of Health Stroke Scale score was 6.6 ± 8.3. Left-sided infarction was observed in 13 patients (33.3%), and insular cortex involvement was observed in 9 patients. Nutritional intake type during CGM was no oral intake in 10, oral intake with drip infusion in 22, and oral intake only in 7 at the initiation of CGM, and 4, 26, and 9, respectively, at the end of CGM. Blood glucose measurement by the pinprick method during CGM was performed 4.0 ± 4.9 times in each AIS patient. Blood glucose levels by pinprick method were well correlated with CGM glucose values (r = .91, P < .001, supplemental data).

Frequencies of Hypoglycemia and Hyperglycemia

Hypoglycemia (<60 mg/dL) was observed in 19 patients (48.7%). The frequency of hypoglycemia during the 72-hour monitoring period was 10.1 ± 15.7%, and the highest quartile of hypoglycemic event in CGM was 7.1%-50.2% (Table 2). A CGM chart in a patient with hypoglycemic events is shown in Figure 1. Hyperglycemia (>180 mg/dL) was observed in 21 patients (53.9%). The frequency of hyperglycemia was 11.9 ± 22.5%, and the highest quartile of hyperglycemia was 5.8%-90.3%. A CGM chart in a patient with hyperglycemic events is shown in Figure 2.

In Table 3, frequencies of hypo- and hyperglycemic events and mean and SD of glucose levels during CGM are shown by daytime and night-time. The frequency of hyperglycemic events and the mean and SD of glucose during CGM were significantly higher in daytime than in night-time, P = .001, P < .001, and P < .001, respectively. The frequency of hypoglycemic events were significantly higher in night-time than in daytime (P < .001).

Table 1. *Patients' characteristics*

	Total (N = 39)
Age, y, mean ± SD	75.9 ± 11.5
Male, N (%)	23 (59.0)
BMI, mean ± SD	21.8 ± 3.7
Comorbidity	
Hypertension, N (%)	34 (87.2)
Dyslipidemia, N (%)	22 (56.4)
Diabetes mellitus, N (%)	12 (30.8)
HbA1c (NGSP, %), mean ± SD	6.2 ± 1.4
Treatment for hyperglycemia during CGM	
None, N (%)	29 (74.4)
Insulin only, N (%)*	5 (12.8)
Oral hypoglycemic agent only, N (%)†	1 (2.6)
Insulin and oral hypoglycemic agents, N (%)‡	4 (10.3)
Acute ischemic stroke	
Subtypes of acute ischemic stroke	
Large-artery atherosclerosis, N (%)	14 (35.9)
Cardioembolism, N (%)	7 (17.9)
Small-vessel occlusion, N (%)	7 (17.9)
Stroke of other determined etiology, N (%)	5 (12.8)
Stroke of undetermined etiology, N (%)	6 (15.4)
Lesion	
Left, N (%)	13 (33.3)
Insular cortex involvement, N (%)	9 (23.1)
Left insular cortex, N (%)	5 (12.8)
NIHSS score, mean ± SD	6.6 ± 8.3
Nutrition during continuous glucose monitoring	
DIV only, N (%)	4 (10.3)
Oral intake/tube feeding (with or without DIV), N (%)	35 (89.7)

Abbreviations: BMI indicates body mass index; CGM, continuous glucose monitoring; DIV, drip infusion into vein; NGSP, National Glycohemoglobin Standardization Program; NIHSS, National Institute of Health Stroke Scale.

*Three people used sliding scale insulin only, and 3 people used sliding scale and fixed-dose insulin.

†The patient was taking a DPP-4 inhibitor.

‡Three people used sliding scale insulin and DPP-4 inhibitors, 1 person used sliding scale insulin, a DPP-4 inhibitor, and a sulfonylurea.

Table 2. *Rates of hypoglycemia and hyperglycemia*

	Total (N = 39)
Patients with hypoglycemia (<60 mg/dL), N (%)	19 (48.7)
Percentage of hypoglycemia (%), mean ± SD	10.1 ± 15.7
Patients with hyperglycemia (>180 mg/dL), N (%)	21 (53.9)
Percentage of hyperglycemia (%), mean ± SD	11.9 ± 22.5

Multivariate Logistic Regression Analyses

Univariate and multivariate logistic regression analyses for the highest quartile of frequencies of hypo- and hyperglycemic events are shown in Tables 4 and 5. For the prediction of hypoglycemic events, only the admission blood glucose level was found to be a significant factor (Table 4). Similarly, only the admission blood glucose level was found to be a significant factor for the prediction of hyperglycemic events (Table 5). In Figure 3, hypoglycemic and hyperglycemic events (% per 72-hour period) are plotted against blood glucose levels at admission. Hypoglycemic events were mainly observed in patients with normoglycemia at admission, and hyperglycemic events were mainly observed in patients with hyperglycemia at admission.

Discussion

When hyperglycemia was detected in the patients in the present study, blood glucose levels were measured as needed, and in most cases, insulin therapy using the sliding scale method was initiated. However, frequent glycemic control was not necessarily performed in patients with normoglycemia at admission and in noninsulin-using patients. In particular, blood glucose measurements were not taken during the night after the patients had gone to sleep. When the FreeStyle Libre Pro was placed for continuous monitoring of blood glucose fluctuations in acute stroke patients, hypo- and hyperglycemic events outside the values recommended by the guidelines were observed.

According to the CGM conducted in the present study, hypoglycemia of less than 60 mg/dL, which requires early correction, was observed at a mean frequency of 10.1 ± 15.7%, and the frequency was significantly higher during night-time. In this study, blood glucose measurement by the pinprick method during CGM was average of 4.0 ± 4.9 times. Since all hypoglycemic events observed by CGM were in patients that presented with normoglycemia at admission, blood glucose levels were not measured during sleep at night, and it was not clinically considered to be a hypoglycemic event. Multivariate logistic regression analysis showed that casual blood glucose levels at admission are significant potential predictors for hypoglycemic events with CGM. These findings suggested that, night-time measurement of blood glucose may be recommended for AIS patients that present with normal-range casual blood glucose levels at admission.

Through CGM observation in the present study, hyperglycemia of 180 mg/dL or more, which requires correction based on the guidelines, was observed in 21 patients (53.9%), and the mean percentage of hyperglycemia was 11.9 ± 22.5%. The results showed that there was a significantly high percentage of hyperglycemia among those with high blood glucose levels at admission.

While there is room for discussion about the cause of hyperglycemia, it is presumed to be associated with the fact that physical stress due to the stroke activates the hypothalamic-pituitary-adrenal system and contributes to insulin resistance, glycogenolysis, and gluconeogenesis.[15] In addition, AIS patients require bed rest and assessment of swallowing function, and in some cases where impaired consciousness is present, there may be periods of time where patients are on nothing-by-mouth or have irregular dietary intakes. In such cases, many patients need to temporarily stop taking previously administered diabetic medications or rapid-acting insulin. We have no choice but using a sliding scale for decisions necessity of oral hypoglycemic agents and fixed insulin dosages. This may have been the reason for the high percentage of hyperglycemia in the acute phase. Since blood glucose levels may remain at a higher level as a stress response during the AIS phase, once dietary intake stabilizes, glycemic control should be stabilized by resuming previous treatment regimens as early as possible and through administration of fixed insulin or diabetic medication.

It is reported so far that hyperglycemia has been related to poor prognosis regardless of whether the patients had diabetes in AIS patients,[3-6] and furthermore, Wada, et al recently reported that not only hyperglycemia but also high blood glucose fluctuation index are related to death or dependency at 3 months in 58 AIS patients.[10] It is also well known that severe or prolonged hypoglycemia can result in permanent brain damage. The present study of CGM found that there are many patients with glucose levels outside the recommended guideline range. Blood glucose levels at admission may be useful for its prediction. Further studies are warranted whether additional blood glucose measurement during the night-time would be effective to prevent hypoglycemia in AIS patients with normoglycemia at admission.

Limitations

The present study had several limitations. The first limitation was the small number of subjects and a single-center study. Second, CGM started from 58.6 ± 41.9 hours after onset, which was slightly delayed from the period between immediately after onset and 24 to 48 hours postonset, which could affect ischemic stroke outcomes. Furthermore, since this was an observational

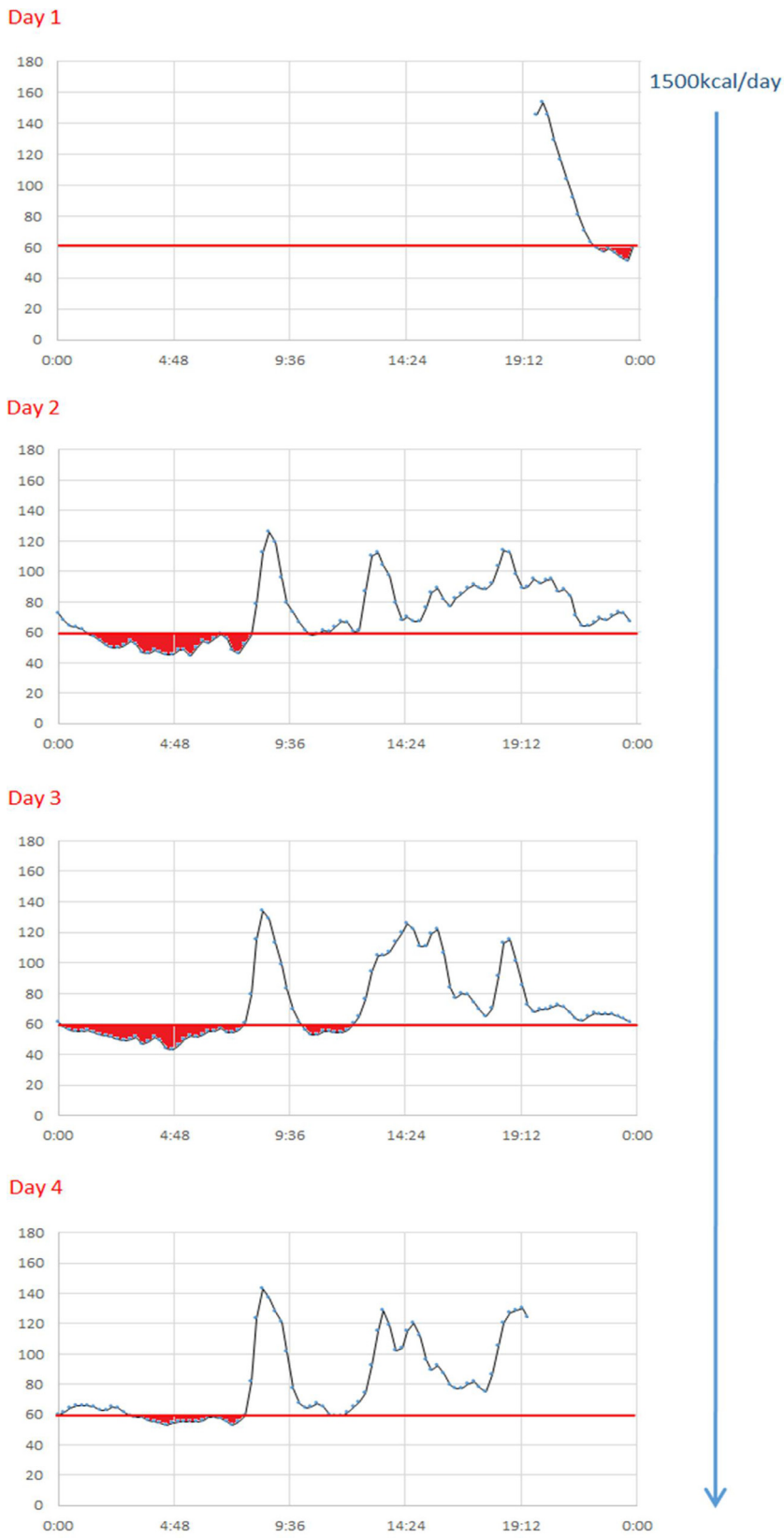

Figure 1. *Continuous glucose monitoring showing hypoglycemic events. A CGM chart of an 87-year-old woman with acute ischemic stroke (NIHSS score, 0; BMI 23.1 kg/m^2; time from onset, 21.7 hours; blood glucose at admission, 83 mg/dL; HbA1c 5.4%). She did not have a history of diabetes mellitus, and oral intake was started. However, CGM shows hypoglycemic events (<60 mg/dL), seen as red areas in the night-time. (Color version of figure is available online.)*

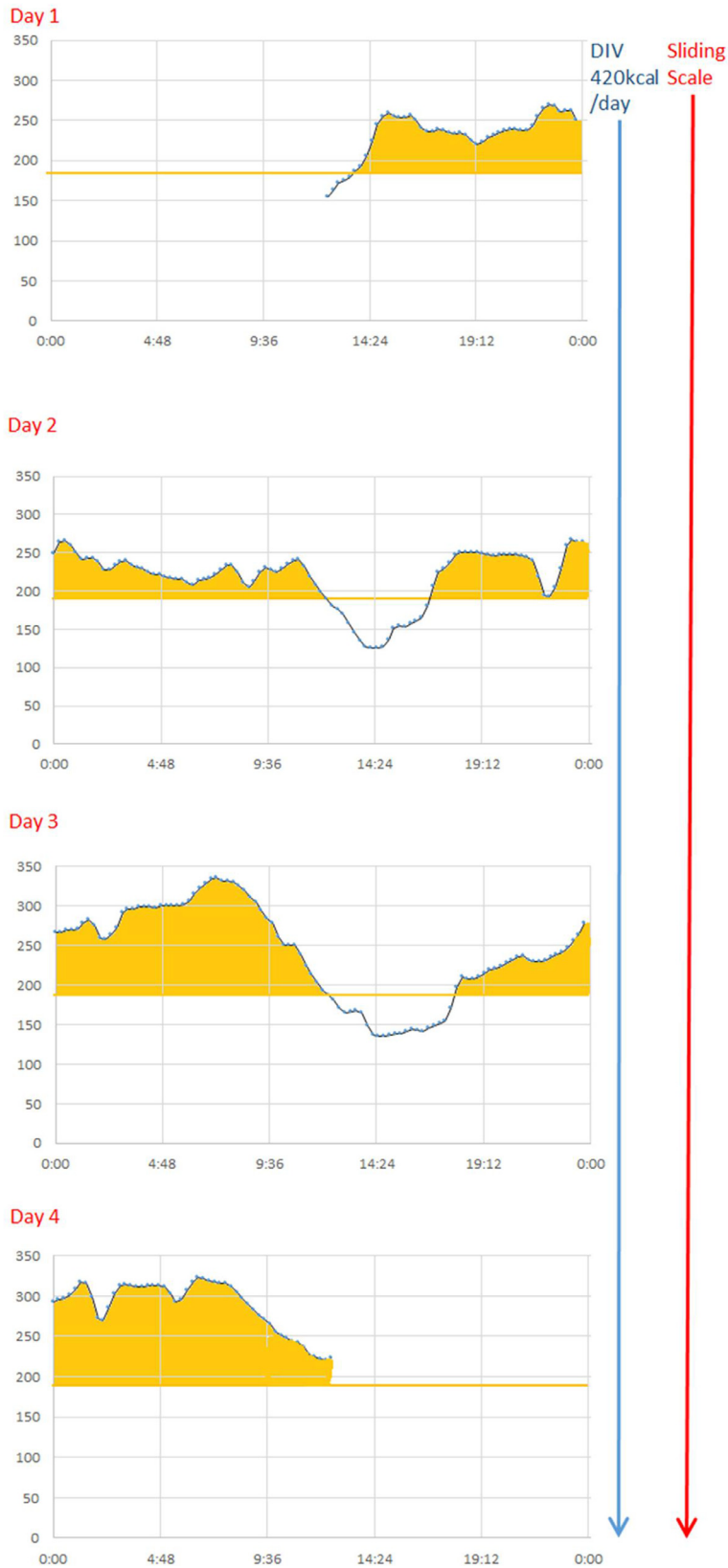

Figure 2. *Continuous glucose monitoring showing hyperglycemic events. A CGM chart of a 70-year-old woman with acute ischemic stroke (NIHSS score, 38; BMI 21.7 kg/m^2; time from onset, 21.5 hours; blood glucose at admission, 236 mg/dL; HbA1c 5.9%). She had a history of diabetes mellitus, hypertension, and dyslipidemia. She had a cardioembolic stroke with large hemispheric infarction caused by left internal carotid occlusion. The patient received peripheral parenteral nutrition only. Since the patient presented with high blood glucose levels at admission, insulin therapy using the sliding scale method was started, targeting a blood glucose level of 140-180 mg/dL as per guidelines. However, hyperglycemic events (>180 mg/dL) are observed (yellow areas) during the 72-hour CGM measurement period. (Color version of figure is available online.)*

Table 3. *Daytime and night-time differences*

	Daytime (06:00-24:00)	Night-time (00:01-05:59)	*P*
Frequency of hypoglycemia (<60 mg/dL), %	7.8 ± 13.2	17.0 ± 26.0	**.000**
Frequency of hyperglycemia (>180 mg/dL), %	13.5 ± 24.1	7.1 ± 20.5	**.001**
Mean blood glucose in CGM, mg/dL	122.5 ± 49.7	99.0 ± 47.2	**.000**
Standard deviation of CGM glucose, mg/dL	29.3 ± 9.9	13.1 ± 8.1	**.000**

Bold value is considered significant P < .05.

Table 4. *Multivariate logistic regression analysis for the highest quartile of frequency of hypoglycemic events*

	Univariate			Multivariate		
	ORs	95% CI	*P*	ORs	95% CI	*P*
Age	1.023	.962-1.087	.468			
Sex	.550	.130-1.087	.416			
BMI	1.032	.853-2.325	.743			
Pre mRS score	1.210	.775-1.891	.402			
NIHSS	.990	.911-1.735	.818			
HT	1.440	.142-14.653	.758			
DM	.455	.082-16.869	.368			
DL	1.583	.377-2.526	.530			
LDL	.968	.937-.999	**.041**	.971	.934-1.009	.130
HDL	.975	.927-.997	.324			
TG	.994	.979-1.025	.427			
GLU	.912	.840-.989	**.027**	.908	.828-.995	**.039**
HbA1c	.371	.100-.994	.140			
CRP	1.120	.896-1.382	.318			

Abbreviations: BMI, mass index; CI, confidence interval; CRP, C-reactive protein; DL, dyslipidemia; DM, diabetes mellitus; GLU, blood glucose; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HT, hypertension; LDL, low-density lipoprotein; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; OR, odds ratio; TG, triglyceride.

Bold value is considered significant *P* < .05.

Table 5. *Multivariate logistic regression analysis for the highest quartile of frequency of hyperglycemic events*

	Univariate			Multivariate		
	ORs	95% CI	*P*	ORs	95% CI	*P*
Age	.993	.937-1.052	.804			
Sex	.550	.130-2.325	.416			
BMI	1.070	.885-1.293	.485			
Pre mRS score	.937	.592-1.482	.780			
NIHSS	1.028	.955-1.108	.460			
HT	1.731	.178-16.869	.637			
DM	3.900	.565-26.926	.167			
HL	1.083	.254-4.630	.914			
LDL	1.023	1.001-1.045	**.045**	1.003	.965-1.043	.875
HDL	.994	.949-1.040	.780			
TG	1.010	.997-1.022	.138			
GLU	1.141	1.001-1.301	**.048**	1.055	1.012-1.099	**.012**
HbA1c	6.951	1.764-27.397	**.006**	1.843	.554-6.128	.319
CRP	.682	.303-1.535	.355			

Abbreviations: BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; DL, dyslipidemia; DM, diabetes mellitus; GLU, blood glucose; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HT, hypertension; mRS, modified Rankin Scale; LDL, low-density lipoprotein; NIHSS, National Institute of Health Stroke Scale; OR, odds ratio; TG, triglyceride.

Bold value is considered significant *P* < .05.

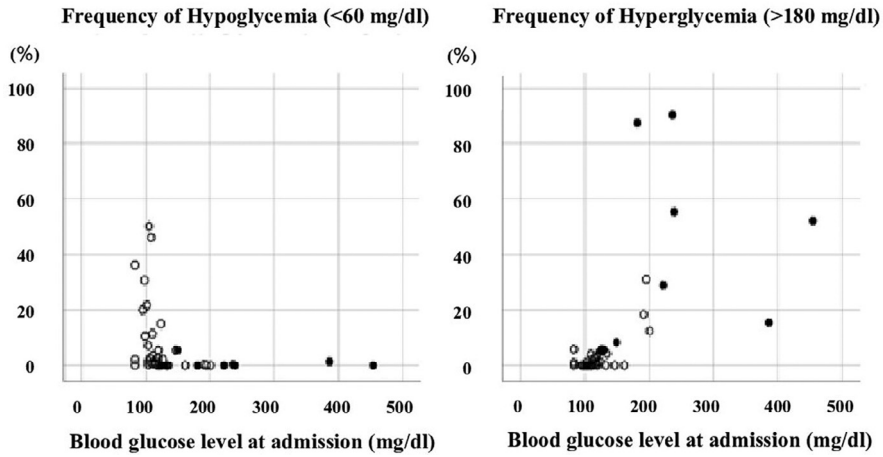

Figure 3. *Hypoglycemia and hyperglycemia in acute ischemic stroke monitored by* continuous glucose monitoring. *The associations of blood glucose levels at admission with the percentages of hypo- and hyperglycemia are shown as a scattergram. Closed circles indicate patients with blood glucose management by insulin injection during continuous glucose monitoring. There is a large percentage of hypoglycemic events in patients within the normal blood glucose range at admission. On the other hand, hyperglycemic events are often observed in patients with high blood glucose levels at admission. Many of these patients received insulin therapy. Not many hypoglycemic events are observed among these patients, and the majority are hyperglycemic events.*

study, whether correction of these hypo- and hyperglycemic events would result in improved outcomes could not be considered.

Author Contributions

Design of the study and data collection were performed by S.N., K.S., N.T., Y.T., N.I., and H.A. Data analysis was performed by S.N. and H.A. Y.H. supervised the conduct of this study and corrected the manuscript.

Declaration of Competing Interest

The authors declare that they have no competing interests.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2019.104346.

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