ORIGINAL RESEARCH

Outcome Prediction in Acute Stroke Patients by Continuous Glucose Monitoring

Shinichi Wada, MD; Sohei Yoshimura, MD, PhD; Manabu Inoue, MD, PhD, FESO, FAHA; Takayuki Matsuki, MD; Shoji Arihiro, MD; Masatoshi Koga, MD, PhD; Takanari Kitazono, MD, PhD; Hisashi Makino, MD, PhD; Kiminori Hosoda, MD, PhD; Masafumi Ihara, MD, PhD, FACP, FAHA; Kazunori Toyoda, MD, PhD, FESO, FAHA

***Background*—**The purpose of this study was to examine the relationships between glucose parameters obtained by continuous glucose monitoring and clinical outcomes in acute stroke patients.

***Methods and Results*—**Consecutive patients with acute ischemic stroke or intracerebral hemorrhage within 24 hours after onset were included. A continuous glucose monitoring device (iPro2) was attached for the initial 72 hours after emergent admission. Eight glucose parameters were obtained from continuous glucose monitoring: maximum, minimum, mean, and SD of blood glucose levels, as well as area under the curve more than 8 mmol/L of blood glucose, distribution time more than 8 mmol/L of blood glucose, coefficient of variation (%CV), and presence of time less than 4 mmol/L over 72 hours. The primary outcome measure was death or dependency at 3 months (modified Rankin Scale score ≥3). One hundred patients with acute ischemic stroke (n=58) or intracerebral hemorrhage (n=42) were included. Blood glucose levels varied between 5.2±1.4 and 11.4±3.2 mmol/L over 72 hours, with area under the curve more than 8 mmol/L of blood glucose of 0.7±1.4 min×mmol/L, distribution time more than 8 mmol/L of blood glucose of 31.7±32.7%, coefficient of variation of 15.5±5.4%, and presence of hypoglycemia in 20% of overall patients. Mean glucose level (adjusted odds ratio, 1.60, 95% confidence interval, 1.12–2.28/1 mmol/L), area under the curve more than 8 mmol/L of blood glucose (2.13, 1.12–4.02/1 min×mmol/L), and distribution time more than 8 mmol/L of blood glucose (1.25, 1.05–1.50/10%) were related to death or dependency for overall patients, as well as for acute ischemic stroke patients (2.05, 1.15–3.65; 2.38, 1.04–5.44; 1.85, 1.10–3.10, respectively).

***Conclusions*—**High mean glucose levels, distribution time more than 8 mmol/L of blood glucose, and areas under the curve more than 8 mmol/L of blood glucose during the initial 72 hours of acute stroke were associated with death or dependency at 3 months. **(*J Am Heart Assoc*. 2018;7:e008744. DOI: 10.1161/JAHA.118.008744.)**

Key Words: acute stroke • continuous glucose monitoring • diabetes mellitus • hyperglycemia • outcome

High blood glucose levels induced by cortisol produced by stress in acute stroke patients are known to be related to initial neurological severity and poor outcome at 3 months after onset.[1–6] However, the detailed dynamic state of blood glucose is affected by various physical conditions and therapeutic processes in the acute phase of stroke, and, accordingly, its association with stroke outcome has not been clarified. Although glycemic variability is known to be associated with the onset of acute coronary syndrome, and hypoglycemia is known to be a predictor of poor outcomes in intensive care unit patients, the relationships between these blood glucose parameters and outcomes are unknown in acute stroke patients.[7–9] The GIST-UK (Glucose-Insulin Stroke Trial-UK) showed no difference in clinical outcomes between acute stroke patients treated with intravenous insulin, potassium, and glucose and those treated with saline.[10] Aggressive

From the Departments of Cerebrovascular Medicine (S.W., S.Y., M. Inoue, T.M., S.A., K.T.), Atherosclerosis and Diabetic Medicine (H.M., K.H.), and Neurology (M. Ihara) and Division of Stroke Care Unit (M.K.), National Cerebral and Cardiovascular Center, Suita, Japan; Department of Medicine and Clinical Science, Graduate School of Medical Science, Kyushu University, Fukuoka, Japan (T.K.).

Accompanying Tables S1 through S5 are available at http://jaha.ahajournals.org/content/7/8/e008744/DC1/embed/inline-supplementary-material-1.pdf

Part of this study was presented orally at the International Stroke Conference, January 24 to 26, 2018, in Los Angeles, CA.

Correspondence to: Sohei Yoshimura, MD, PhD, Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, 5-7-1 Fujishirodai, Suita, Osaka 565-8565, Japan. E-mail: sohei-y@ncvc.go.jp

Received January 30, 2018; accepted March 7, 2018.

Clinical Perspective

What Is New?

- We examine the relationships between glucose parameters obtained by continuous glucose monitoring and clinical outcomes in acute stroke patients.
- Daylong duration of hyperglycemia (≥8 mmol/L) had strong association with higher risk of death or dependency at 3 months and early neurological deterioration within 7 days in overall acute stroke patients.

What Are the Clinical Implications?

- Glucose monitoring using the continuous glucose monitoring during the first days of acute stroke may have prospective of outcome prediction.
- Although aggressive lowering of glucose levels by insulin glargine is not recommended in current guidelines, continuous glucose monitoring may play an important role in future randomized, controlled trials to determine whether to have glucose control for acute stroke.

lowering of blood glucose using insulin was also associated with poor outcomes in another trial.[11,12] Current guidelines did not show any clinical evidence that targeting the blood glucose to a particular level during acute ischemic stroke improves outcomes.[13]

Continuous glucose monitoring (CGM) has recently become commercially available to evaluate the detailed dynamics of blood glucose levels. A CGM device records blood glucose levels every 5 minutes and obtains glucose parameters, and patients are accordingly able to receive intensive glucose management.[14] The aim of this study was to clarify the detailed dynamics of blood glucose levels in acute stroke patients regardless of the presence of diabetes mellitus using a CGM device and to identify the parameters related to death or dependency at 3 months and early neurological deterioration within 7 days after stroke.

Methods

The data, analytical methods, and study materials will not be made available to other researchers for the purpose of reproducing the results or replicating the procedure.

Patients

This was a prospective, single-center, observational study. Consecutive patients with acute ischemic stroke or intracerebral hemorrhage to whom a CGM device could be attached within 24 hours after onset between 9 AM and 12 PM were enrolled. Patients with a known bleeding tendency, limited adherence to stable CGM attachment, indication for emergent hematoma evacuation, or who refused to consent were excluded. This study protocol was approved by the ethical review committee of the National Cerebral and Cardiovascular Center, and written informed consent was obtained from the patients or family members.

Glucose Monitoring

In this study, a CGM device (iPro2; Medtronic, Tokyo, Japan) was used to monitor blood glucose levels. Percent mean absolute relative difference, by which the performance of continuous monitoring sensor is characterized, is 11.0% in the CGM device and the data are accurate enough to use for determination of insulin dosage and detection of hypoglycemia.[15,16] The device was attached to the lower right abdomen with minimally invasive 27-Gauge needles with a length of 10.5 mm introduced subcutaneously. Blood glucose levels were recorded every 5 minutes for up to 72 hours. Blood glucose was also measured from a finger by a glucometer (Medisafe FIT; Terumo, Tokyo, Japan) 4 times a day to calibrate the blood glucose values of the CGM device. Hyperglycemia was defined as a blood glucose level over 8 mmol/L (144 mg/dL), and hypoglycemia was defined as a level below 4 mmol/L (72 mg/dL), based on previous studies.[17–19] Eight blood glucose parameters were evaluated using CGM: (1) maximum, (2) minimum, (3) mean, and (4) SD of blood glucose levels, (5) area under the curve more than 8 mmol/L blood of glucose (8AUC), (6) distribution time more than 8 mmol/L of blood glucose (8time-ratio), (7) coefficient of variation, and (8) presence of a blood glucose level less than 4 mmol/L over 72 hours (Figure). 8AUC was calculated by summing the area values of the time when the blood glucose level was ≥8 mmol/L in Figure. The 8time-ratio was calculated as the ratio of the time when blood glucose exceeded 8 mmol/L divided by 72 hours. Coefficient of variation was calculated as the ratio of SD divided by mean blood glucose. The blood glucose level and hemoglobin A1c of venous blood samples on admission were also examined.

Data Collection

Baseline characteristics of patients, including age, sex, body mass index, current smoking (any), and current drinking (≥2 drinks per day), were recorded. Diabetes mellitus was diagnosed when any of the following criteria were satisfied: fasting blood glucose ≥7 mmol/L or casual blood glucose ≥11.1 mmol/L; blood glucose ≥11.1 mmol/L 2 hours after the 75-g oral glucose tolerance test; taking antidiabetic agents; or previous diagnosis of diabetes mellitus. Hypertension was defined as blood pressure ≥140/90 mm Hg, use of an antihypertensive agent, or previous diagnosis of hypertension. Hyperlipidemia was defined as low-density lipoprotein

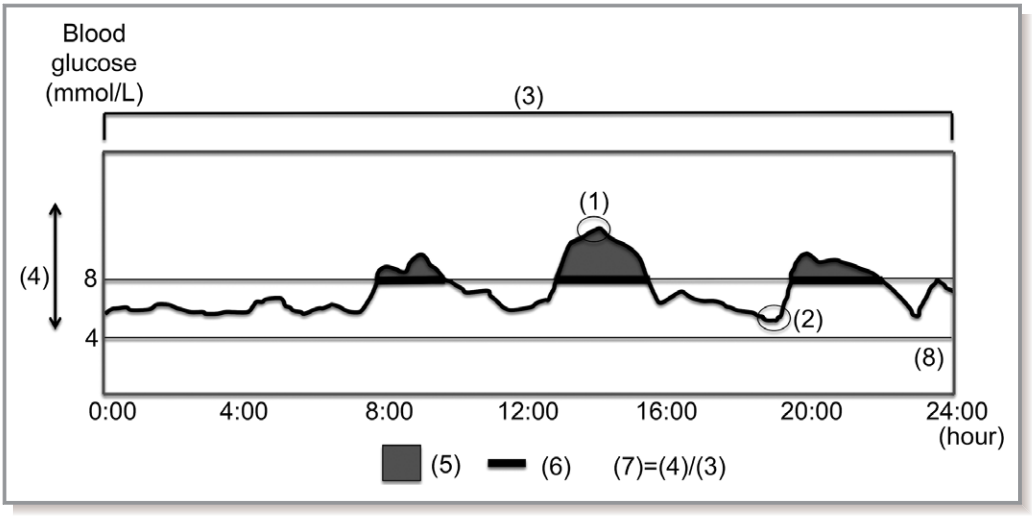

Figure. Eight blood glucose parameters obtained by CGM. (1) Maximum, (2) minimum, (3) mean, and (4) SD of blood glucose during CGM, (5) area under the curve more than 8 mmol/L of blood glucose (8AUC), (6) distribution time more than 8 mmol/L of blood glucose (8time-ratio), (7) coefficient of variation (%CV), and (8) presence of blood glucose level less than 4 mmol/L. 8AUC is calculated by summing area values of the time during which blood glucose level is ≥8 mmol/L in the figure. %CV was calculated as the ratio of SD divided by mean blood glucose. GCM indicates continuous glucose monitoring.

cholesterol ≥140 mg/dL, triglycerides ≥150 mg/dL, high-density lipoprotein cholesterol <40 mg/L, use of antihyperlipidemic agents, or previous diagnosis of dyslipidemia. Trained stroke neurologists assessed the stroke subtype and National Institutes of Health Stroke Scale score on admission and on day 7 from admission and the modified Rankin Scale score 3 months after stroke. Ischemic stroke was verified by magnetic resonance imaging or computed tomography within 24 hours of onset of acute focal brain symptoms. Baseline diffusion-weighted imaging volumes on admission for acute ischemic patients were measured by automated software (RAPID; iSchemaView Inc, Menlo Park, CA), and acute intracerebral hemorrhage size was measured using semiautomated software (MIPAV; http://mipav.cit.nih.gov/) by 2 neurologists blinded to the clinical information. Patients' physical conditions and the therapeutic process during CGM (72 hours) that might affect blood glucose levels were also recorded: high temperature over 37.5°C; peripheral parenteral nutrition without oral intake or tubal feeding; and use of oral antidiabetic agents or insulin.

Outcomes

The primary outcome was death or dependency at 3 months, which was defined as an modified Rankin Scale score of 3 to 6. The secondary outcome was early neurological deterioration, which was defined as an increase of 4 or more points in the National Institutes of Health Stroke Scale scores from baseline within 7 days after admission, excluding patients who died within 7 days.[20,21]

Statistical Analysis

Data are presented as means (SD), median values (interquartile range), or numbers (%). Baseline characteristics and glucose parameters were compared by Student *t* test, Wilcoxon's test, or Pearson's chi-square test, as appropriate. Multivariable analysis was performed using a logistic regression model for death or dependency at 3 months and early neurological deterioration after the index stroke.

Possible confounding factors, including age, sex, past history of coronary artery disease, past history of congestive heart failure, and the factors with $P<0.05$ on univariate analysis, were adjusted for the outcome of death or dependency at 3 months: age, sex, and factors with $P<0.05$ on univariate analysis for early neurological deterioration. Then, the same analysis was repeated for patients with ischemic stroke and those with intracerebral hemorrhage separately. Statistical analysis was conducted using JMP software (version 12.0.1; SAS Institute Inc, Cary, NC).

Results

A total of 100 patients, 58 with ischemic stroke and 42 with intracerebral hemorrhage, were included in this study from October 2015 to June 2016. Table 1 shows the baseline characteristics of all patients. Table 2 shows the blood glucose parameters obtained from CGM. Blood glucose levels varied between 5.2±1.4 and 11.4±3.2 mmol/L over the 72 hours, with mean 8AUC of 0.7±1.4 min×mmol/L, mean 8time-ratio of 31.7±32.7%, mean coefficient of variation of

Table 1. Baseline Characteristics in Overall Stroke Patients

	Overall (n=100)	Death or Dependency		Early Neurological Deterioration	
		Absent (n=64)	Present (n=36)	Absent (n=91)	Present (n=7)
Female	40 (40)	24 (38)	16 (44)	38 (42)	2 (29)
Age, y	70±13	69±13	73±13	70±13	72±12
Body mass index, kg/m^2	22.7±4.5	23.4±4.8	21.5±3.9*	22.7±4.6	22.9±4.2
Current smoking	31 (31)	23 (36)	8 (22)	29 (32)	2 (29)
Current drinking	41 (41)	30 (47)	11 (31)	38 (42)	3 (42)
Intracerebral hemorrhage as the index stroke	42 (42)	19 (27)	23 (64)*	38 (42)	3 (43)
Hypertension	85 (85)	55 (86)	30 (83)	78 (86)	6 (86)
Dyslipidemia	61 (61)	42 (66)	19 (53)	55 (60)	4 (57)
Diabetes mellitus	26 (26)	16 (25)	10 (28)	21 (23)	4 (57)
Past history of coronary artery disease	14 (14)	11 (17)	3 (8)	13 (14)	1 (11)
Past history of congestive heart failure	8 (8)	4 (6)	4 (11)	8 (9)	0
Past history of stroke	13 (13)	8 (13)	5 (14)	13 (14)	0
Premorbid mRS score	0 [0–0]	0 [0–0]	0 [0–0]	0 [0–0]	0 [0–0]
NIHSS score on admission	6 [2–15]	4 [1–9]	14 [8–23]*	6 [2–15]	5 [0–9]
Blood glucose on admission, mmol/L	7.3±2.2	7.1±2.1	7.7±2.4	7.2±2.1	8.6±2.5
HbA1c, %	6.0±0.9	6.0±0.7	6.1±1.1	5.9±0.8	6.8±1.1*
Physical condition and therapeutic process during CGM					
BT over 37.5°C	13 (13)	6 (9)	7 (19)	10 (11)	1 (14)
Peripheral parenteral nutrition	19 (19)	7 (11)	12 (33)*	15 (17)	2 (29)
Usage of glucose-lowering drug	15 (15)	8 (13)	7 (19)	11 (12)	3 (43)

Data are represented as n (%), mean±SD or median [interquartile range]. BT indicates body temperature; CGM, continuous glucose monitoring; HbA1c, hemoglobin A1c; mRS, modified Rankin Scale; NIHSS, indicates National Institutes of Health Stroke Scale.
*P<0.05.

15.5±5.4%, and presence of hypoglycemia in 20% of overall patients.

Analysis of Overall Patients

Patients with death or dependency had a lower body mass index (P=0.03) and higher National Institutes of Health Stroke Scale score on admission (P<0.01), and they more frequently had intracerebral hemorrhage as the index stroke (P<0.01) and peripheral parenteral nutrition (P<0.01; Table 1). Mean glucose level (P<0.01), 8AUC (P<0.01), and 8time-ratio (P<0.01) were higher in patients with death or dependency than in the others (Table 2). On multivariable analysis, higher levels of mean glucose, 8AUC, and 8time-ratio were significantly associated with death or dependency.

In the analysis of the secondary outcome, 2 patients who died within 7 days after admission were excluded. Patients with early neurological deterioration had higher hemoglobin A1c (P=0.01) levels on admission than those without neurological deterioration (Table 1). Mean glucose level (P=0.03), 8AUC (P=0.04), and 8time-ratio (P<0.01) were higher in patients with early neurological deterioration than in those without (Table 3). Only the 8time-ratio was significantly correlated with neurological deterioration on multivariable analysis.

Analysis of Patients With Ischemic Stroke

Patients with death or dependency were older (P=0.02) and had higher National Institutes of Health Stroke Scale scores (P<0.01) and larger diffusion-weighted magnetic resonance imaging lesion volume on admission (P<0.01) than those without death or dependency (Table S1). Mean glucose levels, 8AUC, and 8time-ratio were significantly higher in the death or dependency group than independent patients, and all 3 parameters were related to death or dependency on multivariable analysis (Table 4).

In analysis of early neurological deterioration, mean glucose levels (P=0.02), 8AUC (P=0.02), and 8time-ratio (P<0.01) were higher in patients with early neurological deterioration (Table S2). These 3 glucose parameters were

Table 2. Correlations Between Death or Dependency and Blood Glucose Parameters in Overall Stroke Patients

	Overall (n=100)	Absent (n=64)	Present (n=36)	Crude		Adjusted*	
				Odds Ratio (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value
Maximum, mmol/L (/1 mmol/L)	11.4±3.2	11.1±2.8	11.9±3.8	1.08 (0.95–1.23)	0.24	1.08 (0.92–1.27)	0.33
Minimum, mmol/L (/1 mmol/L)	5.2±1.4	5.0±1.4	5.5±1.4	1.26 (0.94–1.69)	0.12	1.06 (0.73–1.54)	0.75
Mean, mmol/L (/1 mmol/L)	7.8±2.0	7.3±1.6	8.6±2.4†	1.41 (1.11–1.80)	<0.01	1.60 (1.12–2.28)	<0.01
SD, mmol/L (/1 mmol/L)	1.2±0.6	1.2±0.6	1.3±0.7	1.17 (0.60–2.28)	0.64	0.83 (0.30–2.26)	0.71
8AUC, min×mmol/L (/1 min×mmol/L)	0.7±1.4	0.4±0.8	1.3±1.9†	1.78 (1.15–2.75)	<0.01	2.13 (1.12–4.02)	0.01
8time-ratio, % (/10%)	31.7±32.7	23.3±25.4	46.7±38.8†	1.25 (1.09–1.43)	<0.01	1.25 (1.05–1.50)	0.01
Coefficient of variation (/10%)	15.5±5.4	16.2±5.2	14.2±5.6	0.48 (0.21–1.11)	0.08	0.35 (0.12–1.02)	0.05
Presence of blood glucose level ≤4 mmol/L	20 (20%)	16 (25%)	4 (11%)	0.38 (0.11–1.22)	0.08	0.32 (0.07–1.38)	0.11

AUC indicates area under the curve; CI, confidence interval.
*Adjusted by age, sex, body mass index, intracerebral hemorrhage, past history of coronary artery disease, past history of congestive heart failure, National Institutes of Health Stroke Scale score on admission, and peripheral parenteral nutrition.
†*P*<0.05.

related to early neurological deterioration on multivariable analysis.

Analysis of Patients With Intracerebral Hemorrhage

Table S3 shows patients' baseline characteristics, and Tables S4 and S5 show the glucose parameters. No glucose parameters obtained from CGM were related to death or dependency or early neurological deterioration on uni- and multivariable analyses.

Discussion

Relationships between consecutive detailed dynamics of blood glucose levels using a CGM device and clinical outcomes after acute stroke were examined. 8AUC and the 8time-ratio were the most influential factors related to death or dependency at 3 months for overall patients, as well as the ischemic stroke group. The 8time-ratio was also related to neurological deterioration within 7 days after onset. This is the first study to clarify the associations of multiple parameters measured by CGM during the first days of stroke with clinical outcomes.

In previous studies, sustained high blood glucose levels after admission led to poor outcomes.[2–5] However, blood glucose was measured only a few times, and the detailed dynamic state was unknown. The CGM device has recently been used to examine the detailed dynamic state in diabetic patients with simple and safe installation. Baird et al[1] examined blood glucose levels using the CGM in 25 patients with anterior circulation stroke syndrome; only mean blood glucose level was measured as a glucose parameter to examine its relationship to poor outcomes. Ribo et al[22] showed that the longer duration of blood glucose ≥140 mg/dL on the CGM and the longer time to

Table 3. Multivariable Analysis of Early Neurological Deterioration in Overall Stroke Patients

	No Deterioration (n=91)	Deterioration (n=7)	Crude		Adjusted*	
			Odds Ratio (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value
Maximum, mmol/L (/1 mmol/L)	11.1±2.8	13.1±4.9	1.18 (0.96–1.44)	0.13	1.16 (0.92–1.45)	0.21
Minimum, mmol/L (/1 mmol/L)	5.1±1.4	5.4±1.0	1.17 (0.68–2.00)	0.58	1.17 (0.65–2.12)	0.60
Mean, mmol/L (/1 mmol/L)	7.5±1.9	9.1±1.8†	1.35 (1.00–1.82)	0.06	1.10 (0.70–1.74)	0.68
SD, mmol/L (/1 mmol/L)	1.2±0.6	1.2±0.3	1.15 (0.30–4.41)	0.84	0.30 (0.04–2.35)	0.20
8AUC, min×mmol/L (/1 min×mmol/L)	0.6±1.2	1.5±1.2†	1.50 (0.97–2.32)	0.09	1.01 (0.50–2.03)	0.98
8time-ratio, % (/10%)	27.5±29.7	69.6±35.9†	1.42 (1.12–1.82)	<0.01	1.36 (1.01–1.82)	0.04
Coefficient of variation (/10%)	15.6±5.5	13.3±2.3	0.39 (0.07–2.21)	0.26	0.20 (0.03–1.46)	0.08
Presence of blood glucose level ≤4 mmol/L	20 (22%)	0	…	0.07	…	0.10

AUC indicates area under the curve; CI, confidence interval.
*Adjusted by age, sex, hemoglobin A1c.
†*P*<0.05.

Table 4. Multivariable Analysis of Death or Dependency in the Ischemic Stroke Group

	Absent (n=45)	Present (n=13)	Crude		Adjusted*	
			Odds Ratio (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value
Maximum, mmol/L (/1 mmol/L)	11.2±2.8	12.1±3.8	1.10 (0.91–1.32)	0.35	1.02 (0.67–1.55)	0.94
Minimum, mmol/L (/1 mmol/L)	4.9±1.2	5.6±1.5	1.54 (0.94–2.52)	0.08	1.86 (0.66–5.21)	0.19
Mean, mmol/L (/1 mmol/L)	7.2±1.9	9.1±2.8†	1.38 (1.05–1.81)	0.01	2.05 (1.15–3.65)	<0.01
SD, mmol/L (/1 mmol/L)	1.2±0.6	1.3±0.9	1.20 (0.50–2.91)	0.69	1.09 (0.19–6.18)	0.92
8AUC, min×mmol/L (/1 min×mmol/L)	0.4±0.9	1.7±2.3†	1.78 (1.10–2.89)	<0.01	2.38 (1.04–5.44)	0.03
8time-ratio, % (/10%)	20.9±24.5	53.5±41.4†	1.34 (1.10–1.63)	<0.01	1.85 (1.10–3.10)	0.01
Coefficient of variation (/10%)	16.7±5.4	14.1±5.4	0.37 (0.09–1.47)	0.14	0.14 (0.01–2.17)	0.11
Presence of blood glucose level ≤4 mmol/L	11 (24%)	2 (15%)	0.56 (0.11–2.93)	0.48	…	0.07

AUC indicates area under the curve; CI, confidence interval.
*Adjusted by age, sex, past history of coronary artery disease, past history of congestive heart failure, National Institutes of Health Stroke Scale on admission, and diffusion-weighted magnetic resonance image lesion volume on admission.
†*P*<0.05.

middle cerebral artery recanalization after intravenous thrombolysis were related to unfavorable outcomes at 3 months in 47 ischemic stroke patients. Shimoyama et al[23] indicated that mean glucose level, large area under the curve >140 mg/dL, and SD on the CGM were associated with infarct volume growth in 78 ischemic stroke patients with internal carotid artery or middle cerebral artery occlusion.

In acute ischemic stroke patients, hyperglycemia is known to be an independent predictor of larger infarct size, unfavorable outcome, and high risk of mortality.[24] Severity of stroke symptoms and large infarct size leads to high production of cortisol and norepinephrine attributed to stress.[25] Hyperglycemia in the acute stroke phase is a manifestation of relative insulin deficiency, which is related to increased lipolysis.[24] Patients with these factors tend to have hyperglycemia in the acute stroke phase regardless of the presence of diabetes mellitus.[26,27]

This study showed that a high mean blood glucose level and day-long duration of hyperglycemia were related to death or dependency at 3 months. Especially in ischemic stroke patients, day-long duration of hyperglycemia had a strong association with higher risk of the outcome in the hours after acute stroke, accelerating brain damage.[22] Elevation of blood glucose levels caused activation of the coagulant system, suppression of the fibrinolytic system, and production of free radicals.[26,28–31] This elevation may also lead to acidosis, excitatory amino acids, and injury to the blood–brain barrier, which cause ischemic brain damage in animal models and expand ischemic lesions volumetrically.[1,23,25,32] Expanding lesions may lead to production of cortisol and norepinephrine, which worsen hyperglycemia. Persistence of this vicious circle of hyperglycemia might relate to early neurological deterioration within 7 days and worse chronic stroke outcomes. CGM can monitor blood glucose more precisely than the ways in previous trials and may play an important role in future randomized, controlled trials to prove this hypothesis.

There was no relationship between glucose parameters obtained from CGM and death or dependency or early neurological deterioration in the intracerebral hemorrhage group in the present study. Generally, a long duration of hyperglycemia induces edema around the hematoma, causing expansion of cell damage, which leads to the production of more cortisol in intracerebral hemorrhage,[5,33,34] and it is accordingly associated with unfavorable outcomes.[35–37] Thus, the negative findings in the present study might be attributed to the small sample size.

The present study has some limitations. First, the sample size was not large enough, which might cause statistical errors. For example, area under the curve and the time ratio of hypoglycemia could not be examined. Second, the observational study design made the interpretation of the results difficult; it was not possible to determine whether the blood glucose parameters during the initial 72 hours affected clinical outcomes or the neurological fluctuation during the initial 72 hours affected blood glucose dynamics.

Conclusion

8AUC and the 8time-ratio were the most influential factors related to death or dependency at 3 months in overall stroke patients, especially in the ischemic stroke group. The 8time-ratio was also related to neurological deterioration within 7 days after onset. Although aggressive lowering of glucose levels by insulin glargine is not recommended in current guidelines,[13,38] new diabetes mellitus medicines have recently been used to prevent postprandial hyperglycemia.[39,40] To determine whether to use such new therapeutic agents in acute

stroke patients, glucose monitoring using the CGM during the first days of stroke seems to be important.

Author Contributions

Wada, Yoshimura, Inoue, Matsuki, Arihiro, and Makino contributed to the concept and rationale for the study. Wada, Yoshimura, Inoue, and Toyoda contributed to statistical analysis. All authors participated in drafting and approval of the final manuscript and take responsibility for the content and interpretation of this article.

Sources of Funding

The present study was supported by Intramural Research Fund (24-4-3) for Cardiovascular Diseases of the National Cerebral and Cardiovascular Center.

Disclosures

None.

References

1. Baird TA, Parsons MW, Phan T, Butcher KS, Desmond PM, Tress BM, Colman PG, Chambers BR, Davis SM. Persistent post stroke hyperglycemia is independently associated with infarct expansion and worse clinical outcome. *Stroke*. 2003;34:2208–2214.
2. Fuentes B, Castillo J, San José B, Leira R, Serena J, Vivancos J, Davalos A, Nunez AG, Egido J, Diez-Tejedor E; Stroke Project of the Cerebrovascular Diseases Study Group, Spanish Society of Neurology. The prognostic value of capillary glucose levels in acute stroke the GLycemia in Acute Stroke (GLIAS) study. *Stroke*. 2009;40:562–568.
3. Tapia-Perez JH, Gehring S, Zilke R, Schneider T. Effect of increased glucose levels on short-term outcome in hypertensive spontaneous intracerebral hemorrhage. *Clin Neurol Neurosurg*. 2014;118:37–43.
4. Putaala J, Sairanen T, Meretoja A, Lindsberg PJ, Tiainen M, Liebkind R, Strbian D, Atula S, Artto V, Rantanen K, Silvonen P, Piironen K, Curtze S, Happola O, Mustanoja S, Pitkaniemi J, Salonen O, Silvennoinen H, Soinne L, Kuisma M, Tatlisumak T, Kaste M. Post-thrombolytic hyperglycemia and 3-month outcome in acute ischemic stroke. *Cerebrovasc Dis*. 2011;31:83–92.
5. Koga M, Yamagami H, Okuda S, Okada Y, Kimura K, Shiokawa Y, Nakagawara J, Furui E, Hasegawa Y, Kario K, Arihiro S, Sato S, Homma K, Matsuki T, Kinoshita N, Nagatsuka K, Minematsu K, Toyoda K; SAMURAI Study Investigators. Blood glucose levels during the initial 72 h and 3-month functional outcomes in acute intracerebral hemorrhage: the SAMURAI-ICH study. *J Neurol Sci*. 2015;350:75–78.
6. Kataoka S, Gohbara M, Iwahashi N, Sakamaki K, Nakachi T, Akiyama E, Maejima N, Tsukahara K, Hibi K, Kosuge M, Ebina T, Uemura S, Kimura K. Glycemic variability on continuous glucose monitoring system predicts rapid progression of non-culprit lesions in patients with acute coronary syndrome. *Circ J*. 2015;79:2246–2254.
7. Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R. Intensive insulin therapy in critically ill patients. *N Engl J Med*. 2001;345:1359–1367.
8. Kuroda M, Shinke T, Sakaguchi K, Otake H, Takaya T, Hirota Y, Sugiyama D, Nakagawa M, Hariki H, Inoue T, Osue T, Taniguchi Y, Iwasaki M, Nishio R, Kinutani H, Konishi A, Hiranuma N, Takahashi H, Terashita D, Hirata KI. Effect of daily glucose fluctuation on coronary plaque vulnerability in patients pretreated with lipid-lowering therapy: a prospective observational study. *JACC Cardiovasc Interv*. 2015;8:800–811.
9. Bellolio MF, Gilmore RM, Stead LG. Insulin for glycaemic control in acute ischaemic stroke. *Cochrane Database Syst Rev*. 2011;7:CD005346.
10. Gray CS, Hildreth AJ, Sandercock PA, O'Connell JE, Johnston DE, Cartlidge NE, Bamford JM, James OF, Alberti KG; GIST Trialists Collaboration. Glucose-potassium-insulin infusions in the management of post-stroke hyperglycaemia: the UK Glucose Insulin in Stroke Trial (GIST-UK). *Lancet Neurol*. 2007;6:397–406.
11. NICE-SUGAR Study Investigators, Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, Bellomo R, Cook D, Dodek P, Henderson WR, Hebert PC, Heritier S, Heyland DK, McArthur C, McDonald E, Mitchell I, Myburgh JA, Norton R, Potter J, Robinson BG, Ronco JJ. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med*. 2009;360:1283–1297.
12. Sacks DB. Therapy: intensive glucose control in the ICU: is sugar nice? *Nat Rev Endocrinol*. 2009;5:473–474.
13. Jauch EC, Saver JL, Adams HP Jr, Bruno A, Connors JJ, Demaerschalk BM, Khatri P, McMullan PW Jr, Qureshi AI, Rosenfield K, Scott PA, Summers DR, Wang DZ, Wintermark M, Yonas H; American Heart Association Stroke Council; Council on Cardiovascular Nursing; Council on Peripheral Vascular Disease; Council on Clinical Cardiology. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2013;44:870–947.
14. Beck RW, Riddlesworth T, Ruedy K, Ahmann A, Bergenstal R, Haller S, Kollman C, Kruger D, McGill JB, Polonsky W, Toschi E, Wolpert H, Price D; DIAMOND Study Group. Effect of continuous glucose monitoring on glycemic control in adults with type 1 diabetes using insulin injections: the DIAMOND Randomized Clinical Trial. *JAMA*. 2017;317:371–378.
15. Noujaim SE, Horwitz D, Sharma M, Marhoul J. Accuracy requirements for a hypoglycemia detector: an analytical model to evaluate the effects of bias, precision, and rate of glucose change. *J Diabetes Sci Technol*. 2007;1:652–668.
16. Rodbard D. Continuous glucose monitoring: a review of successes, challenges, and opportunities. *Diabetes Technol Ther*. 2016;18(suppl 2):S3–S13.
17. Uyttenboogaart M, Koch MW, Stewart RE, Vroomen PC, Luijckx GJ, De Keyser J. Moderate hyperglycaemia is associated with favourable outcome in acute lacunar stroke. *Brain*. 2007;130:1626–1630.
18. Weir CJ, Murray GD, Dyker AG, Lees KR. Is hyperglycaemia an independent predictor of poor outcome after acute stroke? Results of a long-term follow up study. *BMJ*. 1997;314:1303–1306.
19. McCormick M, Hadley D, McLean JR, Macfarlane JA, Condon B, Muir KW. Randomized, controlled trial of insulin for acute poststroke hyperglycemia. *Ann Neurol*. 2010;67:570–578.
20. Delgado MG, Michel P, Naves M, Maeder P, Reichhart M, Wintermark M, Bogousslavsky J. Early profiles of clinical evolution after intravenous thrombolysis in an unselected stroke population. *J Neurol Neurosurg Psychiatry*. 2010;81:282–285.
21. Cappellari M, Bovi P, Moretto G, Zini A, Nencini P, Sessa M, Furlan M, Pezzini A, Orlandi G, Paciaroni M, Tassinari T, Procaccianti G, Di Lazzaro V, Bettoni L, Gandolfo C, Silvestrelli G, Rasura M, Martin G, Melis M, Calloni MV, Chiodo-Grandi F, Beretta S, Guarino M, Altavista MC, Marcheselli S, Galletti G, Adobbati L, Del Sette M, Mancini A, Orrico D, Monaco S, Cavallini A, Sciolla R, Federico F, Scoditti U, Brusaferri F, Grassa C, Specchio L, Bongioanni MR, Sparaco M, Zampolini M, Greco G, Colombo R, Passarella B, Adami A, Consoli D, Toni D. The THRombolysis and STatins (THRaST) study. *Neurology*. 2013;80:655–661.
22. Ribo M, Molina CA, Delgado P, Rubiera M, Delgado-Mederos R, Rovira A, Munuera J, Alvarez-Sabin J. Hyperglycemia during ischemia rapidly accelerates brain damage in stroke patients treated with tPA. *J Cereb Blood Flow Metab*. 2007;27:1616–1622.
23. Shimoyama T, Kimura K, Uemura J, Saji N, Shibazaki K. Post stroke dysglycemia and acute infarct volume growth: a study using continuous glucose monitoring. *Eur Neurol*. 2016;76:167–174.
24. Piironen K, Putaala J, Rosso C, Samson Y. Glucose and acute stroke: evidence for an interlude. *Stroke*. 2012;43:898–902.
25. Parsons MW, Barber PA, Desmond PM, Baird TA, Darby DG, Byrnes G, Tress BM, Davis SM. Acute hyperglycemia adversely affects stroke outcome: a magnetic resonance imaging and spectroscopy study. *Ann Neurol*. 2002;52:20–28.
26. Lindsberg PJ, Roine RO. Hyperglycemia in acute stroke. *Stroke*. 2004;35:363–364.
27. Capes SE, Hunt D, Malmberg K, Pathak P, Gerstein HC. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. *Stroke*. 2001;32:2426–2432.
28. Kruyt ND, Biessels GJ, Devries JH, Roos YB. Hyperglycaemia in an acute ischemic stroke: pathophysiology and clinical management. *Nat Rev Neurol*. 2010;6:144–155.
29. Robbins NM, Swanson RA. Opposing effects of glucose on stroke and reperfusion injury acidosis, oxidative stress, and energy metabolism. *Stroke*. 2014;45:1881–1886.

30. Barugh AJ, Gray P, Shenkin SD, MacLullich AM, Mead GE. Cortisol levels and the severity and outcomes of acute stroke: a systematic review. *J Neurol*. 2014;261:533–545.

31. Toni D, De Michele M, Fiorelli M, Bastianello S, Camerlingo M, Sacchetti ML, Argentino C, Fieschi C. Influence of hyperglycaemia on infarct size and clinical outcome of acute ischemic stroke patients with intracranial arterial occlusion. *J Neurol Sci*. 1994;123:129–133.

32. Kagansky N, Levy S, Knobler H. The role of hyperglycemia in acute stroke. *Arch Neurol*. 2001;58:1209–1212.

33. Song EC, Chu K, Jeong SW, Jung KH, Kim SH, Kim M, Yoon BW. Hyperglycemia exacerbates brain edema and perihematomal cell death after intracerebral hemorrhage. *Stroke*. 2003;34:2215–2220.

34. Zazulia AR, Videen TO, Powers WJ. Transient focal increase in perihematomal glucose metabolism after acute human intracerebral hemorrhage. *Stroke*. 2009;40:1638–1643.

35. Tan X, He J, Li L, Yang G, Liu H, Tang S, Wang Y. Early hyperglycaemia and the early-term death in patients with spontaneous intracerebral hemorrhage: a meta-analysis. *Intern Med J*. 2014;44:254–260.

36. Saxena A, Anderson CS, Wang X, Sato S, Arima H, Chan E, Munoz-Venturelli P, Delcourt C, Robinson T, Stapf C, Lavados PM, Wang J, Neal B, Chalmers J, Heeley E; INTERACT2 Investigators. Prognostic significance of hyperglycemia in acute intracerebral hemorrhage: the INTERACT2 study. *Stroke*. 2016;47:682–688.

37. Guo X, Li H, Zhang Z, Li S, Zhang L, Zhang J, Han G. Hyperglycemia and mortality risk in patients with primary intracerebral hemorrhage: a meta-analysis. *Mol Neurobiol*. 2016;53:2269–2275.

38. European Stroke Organisation (ESO) Executive Committee; ESO Writing Committee. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. *Cerebrovasc Dis*. 2008;25:457–507.

39. Campbell-Scherer DL, Johnson JA. Exenatide may improve maintenance of HbA1c targets, with less hypoglycaemia, but more early adverse effects when compared with low-dose glimepiride. *Evid Based Med*. 2013;18:e42.

40. McCall AL, Cox DJ, Brodows R, Crean J, Johns D, Kovatchev B. Reduced daily risk of glycemic variability: comparison of exenatide with insulin glargine. *Diabetes Technol Ther*. 2009;11:339–344.

SUPPLEMENTAL MATERIAL

Table S1. Baseline characteristics in ischemic stroke.

	Death or dependency		Neurological deterioration	
	Absent	Present	Absent	Present
	n=45	n=13	n=53	n=4
Female	16 (36)	7 (54)	21 (40)	2 (50)
Age, y	71±12	80±10 *	72±12	79±8
Body mass index, kg/m^2	22.9±3.6	21.2±3.7	22.6±3.7	20.9±1.8
Current smoker	18 (40)	2 (15)	19 (36)	1 (25)
Current drinking	26 (58)	4 (31)	28 (53)	2 (50)
Hypertension	36 (80)	10 (77)	42 (79)	4 (100)
Dyslipidemia	33 (73)	7 (54)	37 (70)	2 (50)
Diabetes mellitus	12 (27)	5 (39)	14 (26)	2 (50)
Past history of coronary artery disease	10 (22)	3 (23)	12 (23)	1 (25)
Past history of congestive heart failure	4 (9)	4 (31)	8 (15)	0
Past history of stroke	5 (11)	3 (23)	8 (15)	0
Premorbid mRS score	0 [0-0]	0 [0-2]	0 [0-0]	0 [0-0]
NIHSS score on admission	3 [1-7]	15 [6-26] *	4 [2-11]	3 [0-6]
Blood glucose on admission, mmol/L	7.2±2.4	8.5±3.2	7.3±2.5	8.7±3.3
HbA1c, %	6.1±0.8	6.3±1.3	6.1±0.9	6.5±0.8
IV rt-PA	17 (38)	2 (15)	18 (34)	1 (25)
Infarct volume, ml	2.4±4.5	52.1±71.0 *	9.6±30.1	3.8±7.5
Intravascular therapy	5 (11)	3 (23)	8 (15)	0

Physical condition and therapeutic process during CGM				
Temperature over 37.5°C	1 (2)	2 (15)	2 (4)	0
Peripheral parenteral nutrition	4 (9)	3 (23)	5 (9)	1 (25)
Usage of glucose-lowering drugs	7 (16)	3 (23)	7 (13)	2 (50)

n (%) or mean ± standard deviation or median [interquartile range]. *P<0.05. mRS: modified Rankin Scale, NIHSS: National Institutes of Health Stroke scale, IV rt-PA: intravenous recombinant tissue plasminogen activator, CGM: continuous glucose monitoring.

Table S2. Multivariable analysis of early neurological deterioration in the ischemic stroke group.

	No deterioration (n=53)	Deterioration (n=4)	Crude		Adjusted†	
			Odds ratio (95%CI)	*P*	Odds ratio (95%CI)	*P*
Maximum, mmol/L (/1 mmol/L)	11.1±2.7	12.1±3.3	1.12 (0.81-1.54)	0.52	1.14 (0.82-1.59)	0.46
Minimum, mmol/L (/1 mmol/L)	5.0±1.2	5.7±1.2	1.63 (0.72-3.69)	0.25	1.57 (0.70-3.52)	0.27
Mean, mmol/L (/1 mmol/L)	7.3±1.9	9.7±1.6 *	1.46 (1.00-2.12)	0.05	2.18 (1.12-4.25)	<0.01
Standard deviation, mmol/L (/1 mmol/L)	1.2±0.6	1.3±0.2	1.16 (0.21-6.32)	0.87	1.28 (0.25-6.63)	0.77
8AUC, min×mmol/L (/1 min×mmol/L)	0.5±1.0	1.8±1.4 *	1.92 (1.03-3.58)	0.05	2.28 (1.10-4.73)	0.03
8time-ratio, % (/10%)	23.1±27.4	78.8±24.9 *	1.61	<0.01	2.22	<0.01

			(1.12-2.30)		(1.11-4.42)	
Coefficient of variation (/10%)	16.2±5.5	12.9±1.1	0.25 (0.02-2.77)	0.21	0.28 (0.03-2.86)	0.24
Presence of blood glucose level ≤ 4 mmol/L	13 (25%)	0	-	0.14	-	0.11

CI: confidence interval, AUC: area under the curve. *P<0.05, †adjusted by age, sex.

Table S3. Baseline characteristics in the intracerebral hemorrhage group.

	Death or dependency		Early neurological deterioration	
	Absent	Present	Absent	Present
	n=19	n=23	n=38	n=3
Female	8 (42)	9 (39)	17 (45)	0
Age, y	65±15	69±13	67±14	62±10
Body mass index, kg/m^2	24.7±6.8	21.6±4.0	22.8±5.7	25.6±5.4
Current smoker	5 (26)	6 (26)	10 (26)	1 (33)
Current drinking	4 (21)	7 (30)	10 (26)	1 (33)
Hypertension	19 (100)	20 (87)	36 (95)	2 (67)
Dyslipidemia	9 (47)	12 (52)	18 (47)	2 (67)
Diabetes mellitus	4 (21)	5 (22)	7 (18)	2 (67)
Past history of coronary artery disease	1 (5)	0	1 (3)	0
Past history of cognitive heart failure	0	0	0	0
Past history of stroke	3 (16)	2 (9)	5 (13)	0
Premorbid mRS score	0 [0-0]	0 [0-0]	0 [0-0]	0 [0-0]
NIHSS score on admission	2 [1-6]	14 [11-16] *	14 [1-17]	9 [0-11]
Blood glucose on admission, mmol/L	6.8±1.2	7.3±1.7	7.0±1.5	8.5±1.6
HbA1c, %	5.7±0.5	6.0±0.9	5.8±0.6	7.1±1.6 *
Hematoma volume, mm^3	9.1±11.8	14.3±11.7	11.2±11.7	20.0±16.1
Physical condition and therapeutic process during CGM				
Temperature over 37.5°C	5 (26)	5 (22)	8 (21)	1 (33)

Peripheral parenteral nutrition	3 (16)	9 (39)	10 (26)	1 (33)
Usage of glucose-lowering drugs	1 (5)	4 (17)	4 (11)	1 (25)

n (%) or mean ± standard deviation or median [interquartile range]. *P<0.05. mRS: modified Rankin Scale, NIHSS: National Institutes of Health Stroke scale, IV rt-PA: intravenous recombinant tissue plasminogen activator, CGM: continuous glucose monitoring.

Table S4. Multivariable analysis of death or dependency outcome in the intracerebral hemorrhage group.

			Crude		Adjusted*	
	Absent (n=19)	Present (n=23)	Odds ratio (95%CI)	*P*	Odds ratio (95%CI)	*P*
Maximum, mmol/L (/1 mmol/L)	10.9±2.5	11.7±3.9	1.08 (0.89-1.32)	0.42	1.06 (0.86-1.30)	0.58
Minimum, mmol/L (/1 mmol/L)	5.3±1.8	5.4±1.4	1.06 (0.73-1.56)	0.75	0.91 (0.58-1.45)	0.70
Mean, mmol/L (/1 mmol/L)	7.4±1.0	8.3±2.1	1.55 (0.92-2.61)	0.05	1.43 (0.72-2.84)	0.29
Standard deviation, mmol/L (/1 mmol/L)	1.1±0.4	1.2±0.6	1.55 (0.45-5.33)	0.48	0.94 (0.20-4.31)	0.94
8 AUC, min×mmol/L (/1 min×mmol/L)	0.4±0.4	1.1±1.6	2.29 (0.78-6.70)	0.04	2.07 (0.51-8.40)	0.26
8 time-ratio, % (/10%)	28.8±27.2	42.9±37.7	1.14	0.17	1.06	0.64

			(0.94-1.38)		(0.84-1.34)	
Coefficient of variation (/10%)	15.0±4.8	14.3±5.8	1.02 (0.98-1.07)	0.59	0.62 (0.17-2.31)	0.47
Presence of blood glucose level ≤ 4 mmol/L	5 (26%)	2 (9%)	0.27 (0.05-1.57)	0.12	0.31 (0.05-2.02)	0.20

CI: confidence interval, AUC: area under the curve. * adjusted by age, sex, past history of coronary artery disease, past history of congestive heart, NIHSS score on admission.

Table S5. Multivariable analysis of early neurological deterioration in the intracerebral hemorrhage group.

	No deterioration (n=38)	Deterioration (n=3)	Crude		Adjusted*	
			Odds ratio (95%CI)	*P*	Odds ratio (95%CI)	*P*
Maximum, mmol/L (/1 mmol/L)	11.1±3.0	14.4±7.1	1.23 (0.94-1.62)	0.15	1.11 (0.72-1.71)	0.63
Minimum, mmol/L (/1 mmol/L)	5.3±1.7	5.0±0.7	0.90 (0.42-1.92)	0.77	0.87 (0.22-3.55)	0.85
Mean, mmol/L (/1 mmol/L)	7.8±1.7	8.4±2.0	1.16 (0.66-2.05)	0.62	0.37 (0.03-4.47)	0.30
Standard deviation, mmol/L (/1 mmol/L)	1.2±0.5	1.2±0.5	1.14 (0.13-10.30)	0.90	0.01 (<0.01-8.51)	0.15
8AUC, min×mmol/L (/1 min×mmol/L)	0.7±1.3	1.1±0.9	1.18 (0.58-2.41)	0.67	0.63 (0.07-5.34)	0.62

8time-ratio, % (/10%)	33.7±32.1	57.3±50.5	1.22 (0.86-1.73)	0.25	0.83 (0.41-1.70)	0.59
Coefficient of variation (/10%)	14.7±5.5	13.8±3.7	0.71 (0.06-8.21)	0.78	0.06 (<0.01-15.70)	0.28
Presence of blood glucose level ≤ 4 mmol/L	7 (18%)	0	-	0.28	-	0.46

CI: confidence interval, AUC: area under the curve. *adjusted by age, sex and HbA1c