Glycemic variability of acute stroke patients and clinical outcomes: a continuous glucose monitoring study

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Abstract

Introduction: Glycemic variability (GV) has been associated with worse prognosis in critically ill patients. We sought to evaluate the potential association between GV indices and clinical outcomes in acute stroke patients.

Methods: Consecutive diabetic and nondiabetic, acute ischemic or hemorrhagic stroke patients underwent regular, standard-of-care finger-prick measurements and continuous glucose monitoring (CGM) for up to 96 h. Thirteen GV indices were obtained from CGM data. Clinical outcomes during hospitalization and follow-up period (90 days) were recorded. Hypoglycemic episodes disclosed by CGM but missed by finger-prick measurements were also documented.

Results: A total of 62 acute stroke patients [48 ischemic and 14 hemorrhagic, median NIHSS score: 9 (IQR: 3–16) points, mean age: 65 ± 10 years, women: 47%, nondiabetic: 79%] were enrolled. GV expressed by higher mean absolute glucose (MAG) values was associated with a lower likelihood of neurological improvement during hospitalization before and after adjusting for potential confounders (OR: 0.135, 95% CI: 0.024–0.751, $p = 0.022$). There was no association of GV indices with 3-month clinical outcomes. During CGM recording, 32 hypoglycemic episodes were detected in 17 nondiabetic patients. None of these episodes were identified by the periodic blood glucose measurements and therefore they were not treated.

Conclusions: Greater GV of acute stroke patients may be related to lower odds of neurological improvement during hospitalization. No association was disclosed between GV indices and 3-month clinical outcomes.

Keywords: acute stroke, clinical outcomes, continuous glucose monitoring, glycemic variability, hypoglycemic episodes, neurological improvement

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Introduction

Poststroke hyperglycemia is a common phenomenon in the acute setting of stroke and has been considered an independent predictor of poor clinical outcomes in both ischemic and hemorrhagic stroke.[1–6] Thus, hyperglycemia management with intensive treatment had been expected to improve clinical outcomes. Despite the initial enthusiasm, randomized controlled clinical trials did not confirm the safety and efficacy of such treatment approaches.[7,8] On the contrary, aggressive protocols with intravenous insulin infusions significantly increased the risk of hypoglycemia, which has been related to adverse functional outcomes in patients with acute ischemic stroke.[9]

By focusing strictly on hyperglycemia and hypoglycemia, however, we might have been overlooking a

third independent component of dysglycemia: glycemic variability (GV), which is defined as the degree of fluctuation in glucose values over time.[10] GV has been correlated with higher mortality risk in critically ill patients, even when mean glucose values are within normal limits.[11,12] GV has been consistently overlooked in relevant randomized controlled clinical trials, although it may be a key reason why intensive glycemic control has failed to demonstrate significant clinical benefit in stroke patients.[13,14] In recent years, there has been a growing interest regarding the role of GV in stroke outcomes in several observational studies.[15–21] Those studies, however, are relatively limited either by the lack of continuous glucose monitoring (CGM) data or by the assessment of only a proportion of the existing GV indices.[22]

In this prospective, cohort study, we examined the association between GV and clinical outcomes in consecutive diabetic and nondiabetic, ischemic, and hemorrhagic acute stroke patients using CGM and calculated GV by measuring 13 different qualitative and quantitative indices. We hypothesized that increased GV in the acute stroke setting is associated with adverse short- and long-term clinical outcomes.

Methods

Consecutive patients with acute ischemic or hemorrhagic stroke were prospectively evaluated at two tertiary stroke centers ('Attikon' University Hospital, National and Kapodistrian University of Athens, Athens, Greece and Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, USA) over a 3-year period. Patients were eligible for inclusion if they experienced acute neurological impairment within the last 48 h, attributable to acute ischemic or hemorrhagic stroke, as was confirmed by neuroimaging evaluation [brain computed tomography (CT) scan or magnetic resonance imaging (MRI) scan]. The patient cohort included both diabetic and nondiabetic patients. Patients with traumatic intracerebral hemorrhage, subarachnoid hemorrhage (aneurysmal or nonaneurysmal), or sub- or epidural hemorrhage were excluded from participation in the study. Other exclusion criteria were patients younger than 18 years old, symptoms onset >48 h from hospital admission, unwillingness to undergo subcutaneous CGM device insertion, or lack of informed consent.

All patients were treated according to standard of care.[23–25] In addition, all patients underwent the following clinical laboratory and imaging examinations, as previously described: serial assessments of stroke severity using National Institute of Health Stroke Scale (NIHSS) score, brain CT scan or MRI scan, full blood count, biochemical blood analysis [baseline glucose values and Hemoglobin A1c (HbA1c) included], electrocardiogram, consecutive blood pressure measurements.[26–29] In cases of ischemic stroke, cardiac ultrasound, 24-h Holter heart rhythm monitoring, carotid duplex ultrasound, and CT or magnetic resonance (MR) brain angiography or transcranial doppler ultrasound were also performed for the etiological classification according to Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification,[30] as previously described.[28] Hemorrhagic strokes were also classified according to most probable etiology.[31] In cases of intracerebral hemorrhage, hematoma volume was measured by two independent certified stroke neurologists according to the ABC/2 formula,[32] as previously described.[26]

Baseline characteristics, including demographics, various vascular risk factors with special interest to diabetes mellitus diagnosis, prestroke treatment, acute stroke treatment, the laboratory and imaging findings, were recorded, as previously described.[26–29] Stroke severity at hospital admission and at discharge was documented using NIHSS score by certified vascular neurologists.[33] Reduction of NIHSS score of 4 or more points between hospital admission and discharge was considered as neurological improvement during hospitalization.[34,35] Increase by any point in NIHSS score at discharge compared with NIHSS at admission was considered as neurological deterioration during hospitalization. In-hospital complications were also recorded: fever, aspiration pneumonia, infection, intubation. Certified vascular neurologists also assessed functional outcomes at 3 months by patient examination, using the modified Rankin scale (mRS).[36] Excellent functional outcome was defined as an mRS score of 0 or 1 and functional independence was defined as an mRS score between 0 and 2.[6]

Glucose measurement and hyperglycemia management were performed according to current international recommendations.[23,37] Each patient was evaluated 4 times daily by finger-prick glucose measurement and subcutaneous insulin was

administered accordingly, in order to achieve a mild hyperglycemic state (between 120 and 180 mg/dl). For hypoglycemia prevention and management, we implemented a nurse-initiated protocol when glucose values were below 70 mg/dl, according to American Diabetes Association recommendations.[38]

In all patients a CGM device (iPro2, Medtronic®, Northridge, CA, USA) was inserted subcutaneously in the lower abdomen within the first 48 h of symptoms initiation. Glucose levels were recorded every 5 min for up to 96 h and were saved in device memory. After the device was removed, data were uploaded and calibrated with the corresponding glucose values derived from finger-prick measurements. As an example, a diagram derived by CGM uploaded data is presented in Supplementary Figure S1. The final data set was edited anonymously in a macro-enabled Excel workbook using EasyGV© software (available free for noncommercial use at https://www.phc.ox.ac.uk/research/technology-outputs/easygv).[39] The EasyGV© was used to calculate the following indices of GV: mean glucose value, standard deviation (SD), M-value, mean amplitude of glucose excursions (MAGE), average daily risk ratio (ADRR), lability index (LI), J-Index, low blood glucose index (LBGI), high blood glucose index (HBGI), continuous overlapping net glycemic action (CONGA), mean of daily differences (MODD), glycemic risk assessment in diabetes equation (GRADE), and mean absolute glucose (MAG).[12,40–48] All definitions and formulas of the GV indices assessed are provided in the Supplementary Table S1.

In the case of continuous glucose measurements, hypoglycemic events were defined as four or more consecutive values of CGM-obtained glucose below 70 mg/dl, which amounted to a total duration of at least 20 min.[49] The hypoglycemic episodes disclosed by CGM but missed by finger-prick measurements were also documented.

The primary outcome of interest was 3-month excellent functional outcome. Secondary outcomes were functional independence at 3 months, mortality at 3 months, in-hospital mortality, neurological deterioration, and neurological improvement during hospitalization. All endpoints' assessments were performed by blinded independent neurologists during hospitalization and in the outpatient setting at 3-month follow-up. In addition, we sought to compare CGM and periodic finger-prick measurements in detecting asymptomatic hypoglycemic events.

The study protocol was approved by both local ethics committees (Protocol No. A.3/6th Committee Meeting/15-05-2018/'Attikon' University Hospital and Beth Israel Deaconess Medical Center Committee on Clinical Investigations, IRB Protocol No. 2014 P-000163) and signed informed consent was obtained from the patient or legal representative before enrollment in all cases. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Statistical analysis

Continuous variables are presented as mean ± SD (normal distribution) and as median with interquartile range (IQR, skewed distribution). Categorical variables are presented as number of patients and the corresponding percentages. Statistical comparisons between two groups were performed using χ^2 test, or in case of small expected frequencies, Fisher's exact test. Continuous variables were compared by the use of the unpaired t test or Mann–Whitney U test, as indicated. Univariable and multivariable binary logistic regression models were used to evaluate the associations of different indices of GV with clinical outcomes before and after adjusting for potential confounders (demographic characteristics, stroke risk factors, stroke severity, in-hospital complications). A cutoff of $p < 0.1$ was used to select variables for inclusion in multivariable analyses that were conducted using backward stepwise selection procedure. In addition, age, sex, and index event were included in multivariable analysis, as they are considered significant potential confounders. To confirm the robustness of multivariable models, we repeated all multivariable analyses using a forward selection procedure. Associations are presented as odds ratios (ORs) with corresponding 95% confidence intervals (CIs). Statistical significance was achieved if the p value was $\leqslant 0.05$ in multivariable logistic regression analyses. The Statistical Package for Social Science (SPSS Inc, Armonk, NY, USA; version 23.0 for Windows) was used for statistical analyses.

Results

The CGM device was inserted successfully to a total of 62 stroke patients (mean age: 65 ± 10 years,

53% men, median NIHSS score on admission: 9, IQR: 3–16) after a median of 32 (IQR: 25–44) h from stroke onset. Thirteen (21%) patients were diabetic. The median duration of monitoring was 70 (IQR: 54–87) h and provided a total of 49,987 glucose measurements for analysis. The baseline characteristics of the study population are presented in Table 1. Forty-eight (77%) strokes were ischemic and 14 (23%) were hemorrhagic. Ischemic strokes were primarily cryptogenic (38%) and cardioembolic (33%), whereas hemorrhagic strokes were hypertension related in the majority of the cases (64%). Median HbA1c was 5.6% (IQR: 5.2–6.0%) and median blood glucose on admission was 118 (IQR: 105–131) mg/dl.

Patients were hospitalized for a median of 10 (IQR: 6–12) days. Three patients died during hospitalization and the in-hospital mortality rate was 5%. Death at 3 months was recorded in six patients (10%). All the rest completed follow-up clinical evaluation at 3 months. Clinical outcomes during hospitalization and at 3 months are presented in Table 2. Thirty patients (48%) presented neurological improvement during hospitalization and the median NIHSS score at discharge was 3 (IQR: 1–8). At 3 months, 34 patients (55%) were functionally independent and 24 patients (39%) presented an excellent functional outcome.

Analysis of CGM-derived data provided evaluation of GV by 13 different indices. Values of each index in all, nondiabetic and diabetic patients are presented in Supplementary Table S2. Diabetic patients had higher mean glucose value, SD, CONGA, J-index, HBGI, GRADE, and ADRR but lower LBGI value compared with nondiabetic patients (all $p < 0.05$).

In the univariate analyses, no statistically significant association was found between GV indices and functional independence or excellent functional outcome at 3 months (all $p > 0.1$; Table 3). No further analysis was performed for death at 3 months and neurological deterioration during hospitalization due to infrequent events (Table 2). Higher ADRR and MAG values, however, were associated with lower likelihood of neurological improvement during hospitalization (Table 4). In multivariable models using backward selection procedure and adjusting for potential confounders (demographics, risk factors, baseline stroke severity, baseline neuroimaging and laboratory findings), MAG emerged as an independent predictor of the likelihood of neurological improvement during hospitalization with an inverse association (OR per 1-unit increase: 0.135, 95% CI: 0.024–0.751, $p = 0.022$; Table 4). We found identical results by repeating the multivariable analyses using forward selection procedure.

None of the GV indices were associated with neurological improvement during hospitalization at a corrected (for multiple comparisons) level of significance: $p = 0.05/13 \approx 0.004$ (unpaired t test after Bonferroni's correction for multiple comparisons; Supplementary Table S3).

Asymptomatic hypoglycemic episodes were detected in 17 patients (27%) during CGM recordings; none of these had been identified with finger-prick measurements. In total, 32 hypoglycemic episodes had gone unrecognized by the standard finger-prick glucose measurements and left untreated in those patients. No symptomatic hypoglycemic episodes were detected by either CGM or finger-prick measurements. Up to six hypoglycemic episodes with a total duration of 18 h were recorded in a single nondiabetic patient, which remained hypoglycemic for more than 27% of the CGM recording. In this patient, the hypoglycemic episodes were recorded almost exclusively during sleep. The prevalence of hypoglycemic episodes was higher in nondiabetic patients (35%) than in diabetic individuals (0%, $p = 0.013$ by Fisher's exact test). Those under-recognized hypoglycemic episodes were not associated with neither 3-month nor in-hospital clinical outcomes (Supplementary Table S4).

Discussion

Our pilot study showed that elevated GV expressed by higher MAG values was associated with a lower likelihood of neurological improvement during hospitalization. Clinical outcomes at 3 months, however, were not related to any of the GV indices measured in our study. This result can be explained by the fact that temporary oxidative stress and endothelial dysfunction promoted by GV may have contributed to short-term cerebrovascular damage and the corresponding lower likelihood of neurological improvement.[50,51] This effect, however, appears not to interfere with long-term clinical outcomes at 3 months. Another potential explanation may be associated with the

Table 1. Baseline characteristics of the study population ($N = 62$).

Variable	Overall
Demographics	
Age, years, mean ± SD	65 ± 10
Female sex, *n* (%)	29 (47)
Index event	
NIHSS score, points, median (IQR)	9 (3–16)
Ischemic stroke, *n* (%)	48 (77)
Large artery atherosclerosis, *n* (% IS)	9 (19)
Cardio embolism, *n* (% IS)	16 (33)
Small vessel occlusion, *n* (% IS)	2 (4)
Other determined etiology, *n* (% IS)	3 (6)
Undetermined etiology, *n* (% IS)	18 (38)
Hemorrhagic stroke, *n* (%)	14 (23)
Hypertension related, *n* (% ICH)	9 (64)
Oral anticoagulant related, *n* (% ICH)	4 (29)
Vascular abnormalities related, *n* (% ICH)	1 (7)
Stroke risk factors	
Diabetes, *n* (%)	13 (21)
Noninsulin dependent, *n* (% DM)	11 (85)
Insulin dependent, *n* (% DM)	2 (15)
Hypertension, *n* (%)	45 (73)
Hyperlipidemia, *n* (%)	47 (76)
Current smoking, *n* (%)	18 (29)
Excessive alcohol intake, *n* (%)	8 (13)
Coronary artery disease, *n* (%)	14 (23)
Previous history of TIA or stroke, *n* (%)	10 (16)
Heart failure, *n* (%)	7 (11)
Valvular disease, *n* (%)	1 (2)
Peripheral arterial disease, *n* (%)	9 (15)
Prestroke treatment	
Antiplatelet, *n* (%)	23 (37)
Anticoagulant, *n* (%)	7 (11)

(Continued)

Table 1. (Continued)

Variable	Overall
Antihypertensive, *n* (%)	32 (52)
Statins, *n* (%)	30 (48)
Acute stroke treatment	
Intravenous thrombolysis, *n* (% IS)	21 (44)
Mechanical thrombectomy, *n* (% IS)	3 (6)
Laboratory findings	
Glucose on admission, mg/dl, median (IQR)	118 (105–131)
Hemoglobin A1c, %, median (IQR)	5.6 (5.2–6)
Low-density lipoprotein, mg/dl, mean ± SD	113 ± 38
Systolic blood pressure, mmHg, median (IQR)	150 (140–165)
Diastolic blood pressure, mmHg, median (IQR)	85 (76–97)
Neuroimaging findings	
Anterior circulation, *n* (%)	54 (87)
Right hemisphere, *n* (%)	31 (50)
Hematoma volume, mm^3, median (IQR)	21 (12–30)

DM, diabetes mellitus; ICH, intracerebral hemorrhage; IS, ischemic stroke; IQR, interquartile range; NIHSS, National Institute of Health Stroke Scale; SD, standard deviation; TIA, transient ischemic attack.

small sample size that may not have allowed the decreased odds of neurological improvement in patients with increased GV to translate into worse functional outcomes at 3 months.

GV has previously been shown to correlate well with oxidative stress, as it was estimated from 24-h urinary excretion rates of free 8-iso prostaglandin F2a.[52] In fact, acute glucose fluctuations expressed by MAG were associated with higher production and urinary excretion of free 8-iso prostaglandin F2a, while no relationship was confirmed between oxidative stress and more traditional hyperglycemic markers, such as fasting plasma glucose, mean glucose, and HbA1c.[52] Thus, increased oxidative stress may represent the link between increased GV during the first hours of ictus and early neurological deterioration occurring during hospitalization. MAG value represents the mean absolute glucose change, counting for all glycemic variations over time. It is calculated by the sum of all differences between consecutive glucose values (even when they are within normal range), divided by the total time of monitoring, measured in hours.[12] MAG has been correlated with short-term outcomes, such as intensive-unit and in-hospital mortality, in critically ill patients.[12]

Clinical outcomes at 3 months were not associated with any of the GV indices measured in our study. On the contrary, Wada and colleagues[20] showed that high mean glucose levels, distribution time with blood glucose values more than 8 mmol/L, and areas under the curve presenting blood glucose values more than 8 mmol/L during the initial 72 h of acute stroke were associated with death or dependency at 3 months. All of the associated factors, however, reflected a hyperglycemic state that has previously been correlated with adverse clinical outcomes in stroke.[1,53–55] GV indices that reflected glucose fluctuations at both hyperglycemic and hypoglycemic values were not assessed in the Japanese study. Also difference in sample size (62 *versus* 100 patients), study population (Caucasians and African Americans *versus* Asians), and baseline stroke

Table 2. Clinical outcomes during hospitalization and at 3 months.

Variable	Overall
During hospitalization	
Complications	
Death, *n* (%)	3 (5)
Fever, *n* (%)	20 (32)
Infection, *n* (%)	19 (31)
Aspiration pneumonia, *n* (%)	10 (16)
Intubation, *n* (%)	7 (11)
Clinical outcomes	
Exit NIHSS Score, points, median (IQR)	3 (1–8)
Neurological deterioration, *n* (%)	7 (11)
Neurological improvement, *n* (%)	30 (48)
At 3 months	
Clinical outcomes	
mRS score, median (IQR)	2 (1–4)
Death, *n* (%)	6 (10)
Functional independence, *n* (%)	34 (55)
Excellent functional outcome, *n* (%)	24 (39)

IQR, interquartile range; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale.

severity (9 *versus* 6 points in NIHSS score) may account for the discrepant findings between our and the report by Wada and colleagues.[20]

Our pilot study suggests an excellent feasibility and tolerability of CGM in the acute stroke setting. CGM devices were successfully inserted in 62 patients without any adverse event, such as skin irritation or subcutaneous hematomas, even in the subgroup of patients that received intravenous thrombolysis (34%). Only few studies have implemented CGM recordings in order to measure GV and investigate its association with acute or short-term stroke outcomes.[19,20,56] Those studies, however, calculated only a proportion of existing GV indices that are valid and widely used for GV assessment.[57–59] In our study, we used EasyGV© software that provided 13 quantitative and qualitative GV markers.[39] All of these markers were evaluated for possible associations with stroke outcomes during hospitalization and at 3 months.

GV indices were significantly different between diabetic and nondiabetic patients of our cohort. This should be expected because diabetic patients and patients with impaired blood glucose regulation have more pronounced glucose fluctuations and intraday glycemic excursions.[58,60] In our cohort, nondiabetic patients had GV indices values within the proposed normal reference ranges for Caucasians patients.[39] CGM, however, disclosed 32 hypoglycemic events that had gone unrecognized by the periodic finger-prick glucose measurements. All hypoglycemic episodes were recorded in the subgroup of nondiabetic patients. This finding could be partially attributed to dysphagia and food deprivation in the first days after stroke that may lead to hypoglycemia even in the absence of insulin treatment or history of diabetes mellitus.[61] Despite that insulin treatment was not recorded in our study, such a finding would suggest for careful glycemia management in this patient subgroup. We also postulate that reactive endogenous hyperinsulinemia and insulin resistance may be a preexisting and predisposing factor for endothelial damage in this population. Characteristically, antidiabetic medications that do not increase GV, such as pioglitazone, have already proven beneficial for secondary stroke prevention in patients with diabetes mellitus, prediabetes, and insulin resistance as well.[62]

During those under-recognized hypoglycemic events, glucose values were below 70 mg/dl, but no patient exhibited severe hypoglycemia with glucose values below 40 mg/dl. Although this could be a potential explanation for hypoglycemic episodes being asymptomatic and without significant association with poststroke functional outcomes, it has been previously reported that glucose values lower than 67 mg/dL within the first 24 h of ictus have been related to adverse functional outcomes in patients with acute ischemic stroke.[9] Another reason for the lack of association between under-recognized hypoglycemic events and clinical outcomes may be attributed to the low sample size. The use of improved CGM sensors that do not require calibration and instantly provide glucose values may help identify hypoglycemic episodes and other glycemic excursions in real time and guide a more personalized hyperglycemia management in the acute stroke setting.[63] Moreover, CGM has been

Table 3. Univariable logistic regression analyses depicting the associations of GV indices with functional outcomes at 3 months.

Variable	Mean Glu	SD	CONGA	Li	J-index	LBGI	HBGI	GRADE	MODD	MAGE	ADRR	M-value	MAG
	Odds ratio (95% CI)												
Functional independence	1.202 (0.844–1.712)	1.032 (0.428–2.489)	1.274 (0.867–1.874)	0.841 (0.483–1.466)	1.024 (0.978–1.073)	1.017 (0.770–1.343)	1.116 (0.919–1.357)	1.124 (0.924–1.369)	1.460 (0.649–3.284)	0.879 (0.566–1.367)	1.033 (0.945–1.129)	1.075 (0.967–1.195)	1.053 (0.388–2.854)
Excellent functional outcome	1.167 (0.803–1.696)	1.306 (0.500–3.413)	1.213 (0.809–1.820)	1.092 (0.632–1.889)	1.024 (0.972–1.078)	1.008 (0.757–1.342)	1.110 (0.888–1.387)	1.089 (0.885–1.341)	1.362 (0.562–3.302)	1.015 (0.653–1.580)	1.010 (0.923–1.106)	1.049 (0.945–1.163)	1.241 (0.440–3.502)

ADRR, average daily risk ratio; CI, confidence interval; CONGA, continuous overlapping net glycemic action; Glu, glucose; GRADE, glycemic risk assessment in diabetes equation; GV, glycemic variability; HBGI, high blood glucose index; LBGI, low blood glucose index; Li, lability index; MAG, mean amplitude of glucose excursions; MODD, mean of daily differences; SD, standard deviation.

approved for nonadjuvant use, meaning that insulin treatment can be administered based on CGM-derived data without confirmatory blood glucose measurements.[64] CGM sensors combined with closed-loop systems of insulin or dual-hormone (insulin or glucagon) delivery may act as an 'artificial pancreas' and appear as an attractive option for the optimization of glycemia management in acute stroke patients.[65] The safety and efficacy of the implementation of such an integrated method in the setting of a stroke unit remain to be explored in future studies.

Certain limitations of the present pilot study need to be acknowledged. The sample size of the study was limited ($N=62$) and the performed analyses are exploratory and may serve for hypothesis generation. Unwillingness to undergo subcutaneous CGM device insertion was the main reason of the limited recruitment. Moreover, only 13 patients (21%) were recruited within 24 h after symptoms onset, when oxidative stress and GV may have been more pronounced and possibly related to functional outcomes. In addition, data about insulin treatment and feeding status of patients during hospitalization, which could have explained glucose fluctuations and hypoglycemic events, were not available. Because our primary aim was to identify possible associations between stroke outcomes and GV, irrespective of the underlying mechanisms that may have led to the glycemic excursions, however, this limitation seems unlikely to have confounded our results. Furthermore, data regarding acetaminophen use, which can interfere with CGM sensing, were not prospectively collected.[66] Moreover, the duration of CGM recording was no more than 96 h and different values of GV indices could have been calculated, if a more prolonged monitoring were undertaken. Another study that evaluated poststroke hyperglycemia through CGM proposed that a minimum of 72 h of CGM poststroke should be performed.[67] In fact, we have studied CGM for a more prolonged period compared with other stroke studies that have investigated the association of GV with clinical outcomes. It should also be noted that, due to the limited sample, we conducted no subgroup analyses evaluating the association of GV indices with early outcomes in specific stroke subgroups according to etiopathogenic mechanism, nor we adjusted for infarct or hematoma volume in the subgroups of patients with ischemic stroke or intracerebral hemorrhage accordingly. Last, none of the 13 GV indices were associated

Table 4. Univariable and multivariable logistic regression analyses depicting the associations of GV indices, baseline characteristics, and in-hospital complications with the likelihood of neurological improvement during hospitalization.

Variable	Univariable logistic regression analysis		Multivariable logistic regression analysis[a]	
	Odds ratio (95% CI)	*p*	Odds ratio (95% CI)	*p*
GV indices				
Mean glucose	0.724 (0.487–1.079)	0.113		
SD	0.532 (0.193–1.473)	0.225		
CONGA	0.731 (0.481–1.110)	0.141		
Li	0.792 (0.448–1.4)	0.422		
J-index	0.959 (0.906–1.016)	0.156		
LBGI	1.193 (0.877–1.623)	0.262		
HBGI	0.897 (0.731–1.101)	0.299		
GRADE	0.865 (0.7–1.069)	0.179		
MODD	0.590 (0.224–1.554)	0.286		
MAGE	0.759 (0.48–1.2)	0.238		
ADRR	0.843 (0.722–0.985)	0.032	0.924 (0.743–1.148)	0.160
M-value	1.010 (0.938–1.087)	0.79		
MAG	0.333 (0.108–1.029)	0.056	0.135 (0.024–0.751)	0.022**
Baseline characteristics				
Age	1.003 (0.956–1.053)	0.891	1.018 (0.949–1.091)	0.353
Gender	1.308 (0.481–3.558)	0.599	0.771 (0.195–3.041)	0.498
Index event	0.338 (0.093–1.231)	0.1	0.301 (0.054–1.667)	0.312
Diabetes	0.393 (0.107–1.449)	0.161		
Hypertension	1.076 (0.352–3.290)	0.898		
Hyperlipidemia	2.273 (0.673–7.674)	0.186		
Smoking	1.5 (0.498–4.519)	0.471		
Alcohol	1.933 (0.419–8.911)	0.398		
Coronary artery disease	1.087 (0.330–3.576)	0.891		
Previous history of stroke	1.080 (0.279–4.181)	0.911		
Heart failure	1.487 (0.304–7.277)	0.624		
Peripheral arterial disease	0.831 (0.201–3.440)	0.798		
Antiplatelet pretreatment	0.551 (0.193–1.571)	0.265		

(Continued)

Table 4. (Continued)

Variable	Univariable logistic regression analysis		Multivariable logistic regression analysis[a]	
	Odds ratio (95% CI)	*p*	Odds ratio (95% CI)	*p*
Anticoagulant pretreatment	0.386 (0.069–2.16)	0.278		
Antihypertensive pretreatment	1.482 (0.544–4.036)	0.441		
Statin pretreatment	1.133 (0.418–3.072)	0.806		
Glucose on admission	0.990 (0.975–1.005)	0.190		
HbA1c	0.507 (0.257–1.001)	0.05	0.541 (0.245–1.196)	0.107
LDL	0.998 (0.985–1.012)	0.778		
SBP	0.991 (0.971–1.012)	0.4		
DBP	0.997 (0.971–1.023)	0.811		
Stroke of anterior circulation	0.6 (0.13–2.764)	0.512		
Stroke in right hemisphere	2.192 (0.794–6.051)	0.130		
In-hospital complications				
Fever	1.1 (0.379–3.192)	0.861		
Infection	0.943 (0.32–2.779)	0.915		
Aspiration	1.75 (0.441–6.94)	0.426		
Intubation	0.386 (0.069–2.160)	0.386		

ADRR, average daily risk ratio; CI, confidence interval; CONGA, continuous overlapping net glycemic action; DBP, diastolic blood pressure; GRADE, glycemic risk assessment in diabetes equation; GV, glycemic variability; HbA1c, Hemoglobin A1c; HBGI, high blood glucose index; LBGI, low blood glucose index; LDL, low-density lipoprotein; Li, lability index; MAG, mean absolute glucose; MAGE, mean amplitude of glucose excursions; MODD, mean of daily differences; NIHSS, National Institute of Health Stroke Scale; SBP, systolic blood pressure; SD, standard deviation.
[a]Age, sex, index event, and every variable presenting cutoff value of $p < 0.1$ in the univariate analysis were used for selection of candidate variables for inclusion in multivariable logistic regression models. NIHSS score at admission was not included in this analysis, as the outcome (neurological improvement during hospitalization) is a composite of both NIHSS score at admission and NIHSS score at discharge.
**Indicates statistical significance, p value < 0.05.

with neurological improvement during hospitalization at a corrected (for multiple comparisons) level of significance of $p = 0.05/13 \approx 0.004$ (unpaired t test after Bonferroni's correction for multiple comparisons) and our results require further validation in larger studies.

Conclusions

GV was calculated during CGM recording in acute stroke patients and was expressed by 13 different indices. Elevated GV as indicated by higher MAG values was independently associated with lower likelihood of neurological improvement during hospitalization in acute stroke patients. ADRR index and HbA1c value were also associated with neurological improvement in the univariate analysis, but after adjusting for confounders they did not retain their statistical significance. No GV index was related to 3-month clinical outcomes, pointing to a more short-term impact of GV on early poststroke neurological status. CGM recording detected several hypoglycemic episodes in the nondiabetic stroke patients that were missed by the periodic blood glucose measurements, underscoring that glycemia management in the acute stroke setting should be further optimized. Larger multicenter studies are required to

further investigate the validity of these preliminary observations and determine the potential detrimental effects of increased MAG values on early clinical outcomes of acute stroke patients.

Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethics statement and data availability

The study protocol was approved by the Ethics Committee of 'Attikon' University Hospital (Protocol No. A.3/6th Committee Meeting/15-05-2018) and the Beth Israel Deaconess Medical Center Committee on Clinical Investigations (IRB Protocol No. 2014 P-000163). Written informed consent was obtained from all participants before enrollment in the study. All procedures followed were in accordance with the Helsinki Declaration. The studata are available from the corresponding author upon reasonable request

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Supplemental material

Supplemental material for this article is available online.

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