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Clinical Study

Higher Blood Glucose within the Normal Range Is Associated with More Severe Strokes

Rolf J. Martin,[1] Rajiv R. Ratan,[1] Michael J. Reding,[2] and Tom S. Olsen[2,3]

[1] *Burke/Cornell Medical Research Institute, White Plains, NY 10605, USA*
[2] *The Stroke Unit, Burke Rehabilitation Hospital, White Plains, NY 10605, USA*
[3] *The Stroke Unit, Frederiksberg University Hospital, 2000 Frederiksberg, Denmark*

Correspondence should be addressed to Tom S. Olsen, tso@dadlnet.dk

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Background. Higher fasting blood glucose (FBG) concentrations in the hyperglycemic range are associated with more severe strokes. Whether this association also extends into patients with FBG in the normoglycemic range is unclear. We studied the association of stroke severity and FBG in normoglycemic patients with ischemic stroke in a median of 7 days after stroke when the initial glycemic stress response has resolved. *Method and Material*. Included were 361 nondiabetic ischemic stroke patients with admission fasting blood glucose within 70–130 mg/dL admitted into an acute stroke rehabilitation unit in a median of 7 days after stroke. Data including neuroimaging, vital signs, cardiovascular risk factors, and admission functional independence measure (AFIM) were recorded prospectively. *Results*. FBG correlated with stroke severity in the normoglycemic 70–130 mg/dL range (FBG-AFIM correlation coefficient -0.17; $P = 0.003$). Odds ratio for more severe injury (below average AFIM score) was 2.02 for patients with FBG 110–130 mg/dL compared to FBG 70–90 mg/dL (95% confidence interval 1.10–3.73, $P = 0.022$). Each mg/dL increase in FBG was associated with an average decrease of 0.25 FIM points. In a multiple linear regression model, FBG was associated with more severe stroke ($P = 0.002$). *Conclusion*. One week after ischemic stroke, FBG within the normoglycemic range was associated with stroke severity.

1. Introduction

Animal models have provided evidence of a deleterious effect of hyperglycemia on ischemic brain damage [1–5], and hyperglycemia has been identified as a predictor of poorer outcome in an increasing number of observational studies [6–13]. The mechanism by which elevated blood glucose augments ischemic brain injury is not fully understood. The most consistent finding in experimental ischemic brain injury is the association of hyperglycemia with accumulation of lactate and acidosis of the ischemic brain tissue [14–16], but several other potentially harmful biochemical processes working alone or in concert have been proposed [1, 2, 14, 17]. For the most part, the fate of the ischemic brain tissue is determined within the very first few hours after the occlusive event when a large penumbra still prevails [18]. Hence, glucose concentration at the time of the occlusive event may influence the metabolic milieu in the penumbra and thereby the amount of brain tissue undergoing irreversible tissue necrosis as the result of occlusion.

Blood glucose (BG) is usually increased in the hours after a stroke most probably as the result of a stress response to the stroke event [12, 19–21]. However, within a week at least, BG again declines and reaches a stable level [19–22]. Most studies point to an association between initial stroke severity and hyperglycemia on admission to hospital [7, 23, 24], but there are no studies on the association between stroke severity and BG concentrations within the normoglycemic range. Available studies have hitherto used blood samples drawn in the hours after stroke when BG is elevated and therefore do not directly reflect BG concentration at the time of the stroke event [7, 23, 24]. On the premise that FBG measured about one week after stroke (when the stress response has resolved) [22] is representative of the patient's habitual BG at the time of the stroke we studied the association of stroke severity and FBG measured about one week after stroke, in

a cohort of 361 nondiabetic stroke patients with FBG within the normoglycemic range 70–130 mg/dL [25].

2. Methods and Material

The study is based on data from the Burke Rehabilitation Hospital Stroke Database. This database includes information on all patients referred for rehabilitation after stroke from January 2005 to July 2008. Patients were included in the rehabilitation program if they were deemed medically stable, were able to engage in the rehabilitation program, and had a reasonable expectation of making functional gains. Admission patient data were recorded prospectively in a computerized hospital record by rehabilitation team members. Data accuracy and security were checked routinely by the medical records department. The diagnosis of stroke was based on World Health Organization criteria [26] with confirmative neuroimaging studies in each case.

For this study, the following data were extracted from the database:

(i) age, gender, days since stroke, and ethnicity (Caucasian/non-Caucasian),

(ii) admission functional independence measure (AFIM) [27]: AFIM measures mobility, activities of daily living, cognition, and functional communication on an 18 (worst)–126 (best) scale,

(iii) admission blood pressure (BP), admission infrared tympanic membrane temperature,

(iv) cardiovascular risk factors known before admission or diagnosed during hospital stay: arterial hypertension, diabetes mellitus, heart disease including previous myocardial infarction, coronary atherosclerosis, and cardiac heart failure, atrial fibrillation, and body mass index (BMI),

(v) laboratory values: fasting plasma BG,

(vi) type of stroke according to CT/MR imaging: ischemic stroke or hemorrhagic stroke.

Diabetes was diagnosed according to the recommendations of the American Diabetes Association [25]. Hyperglycemia was defined as fasting blood glucose >130 mg/dL; hypoglycemia as blood glucose <70 mg/dL.

Included in the study were nondiabetic patients with FBG in the normal range of 70–130 mg/dL. Patients with FBG outside this range and patients with diabetes were excluded from the study. Patients admitted more than 30 days after stroke were not included in the study.

The study was performed as part of continuous quality improvement (CQI) mandated by the Joint Commission for Accreditation of Hospitals. The CQI objective was to assess adequacy of glycemic control on our stroke rehabilitation units.

2.1. Statistics. The data set was prepared by isolating all ischemic stroke records in the database [ICD9 codes 433-434] and then excluding records according to the following criteria: glucose below 70 or above 130 mg/dL or no glucose value entered, FIM change/day below zero or above 3.5 and days since injury greater than 30 (to exclude atypical patients), a diagnosis of diabetes or diabetic complications [ICD9 codes 250, 357, or 362], or any of the following glucose-lowering medications: Glucophage, Glucophage XR, Humulin R, Humulin N, Lantus, Diabeta, Glucotrol, Glucotrol XL, and Januvia.

AFIM scores and glucose concentrations in this data set were not normally distributed according to Shapiro-Wilk, Anderson-Darling, and Kolmogorov-Smirnov tests of normality (P values for each normality test were 0.000). Injury severity and glucose scores were therefore transformed into ranks and into normally distributed values that retained the original average and standard deviation. Parametric (t-test, multiple linear regression) and nonparametric (Mann-Whitney, Kolmogorov-Smirnov) statistical tests were then employed to determine if glucose-injury severity relationships were significant in both original and transformed data sets at 95% confidence. Parametric and nonparametric results were similar for the original and each transformed data set.

Multiple linear regression results (Wessa, 2009, version 1.1.23-r3, Leuven, Belgium and SPSS Statistics ver. 17.0,) were confirmed by Soft Independent Modelling of Class Analogy (SIMCA P-12, Umetrics, Kinnelon, NJ, US), a multivariate analysis method that excludes data components which decrease the cross-validation prediction accuracy coefficient (Q^2). Multicollinearity that might significantly affect regression results was ruled out by examining variance inflation factors (VIFs) for each independent variable, where the VIF for each independent variable is $1/(1 - R^2)$, and R^2 is the coefficient of determination for the regression equation relating each independent variable to the other independent variables. All VIFs were below 1.5, so by this measure of multicollinearity, there is no reason for concern.

Associations between FBG and days since injury, temperature, PEG (percutaneous endoscopic gastrostomy) tube feeding, and diuretics (furosemide, hydrochlorothiazide, spironolactone, torsemide, bumetanide, and metolazone) were also checked and found to be insignificant. FBG was measured in the early morning when patient activity levels are very low, so activity also can be discounted as a possible confounding factor.

To further assess the possible influence of the days-since-injury range chosen, glucose and AFIM levels and glucose-AFIM correlations were also determined for 0–20, 5–25, 10–30, 15–35, 20–40, 25–45, and 30–50 days since injury. Strong glucose-AFIM correlations were observed regardless of the range chosen. The range 0–30 is reported because it most closely represents the Burke ischemic stroke patient population.

3. Results

A total of 361 nondiabetic patients with FBG within the range of 70–130 mg/dL were included in the study. Descriptive data of these patients regarding age, gender, BMI, ethnic group, AFIM, days since stroke, BP, body temperature, heart disease, atrial fibrillation, and hypertension are listed in Table 1.

Table 1: Basic characteristics of the patients.

No. of patients	361
Age, years (SD)	75.0 (12.9)
Gender, female (%)	188 (52.1)
Ethnic group (% Caucasian)	283 (78.4)
BMI (SD)	25.24 (5.2)
Average days since onset (median, SD)	9.4 (7, 6.2)
Initial stroke severity, admission FIM (SD)	55.7 (21.0)
Blood pressure, systolic, mmHg (SD)	132 (20)
Body temperature, degrees Fahrenheit (SD)	97.5 (1.1)
Body temperature, degrees Celsius (SD)	36.4 (0.6)
Atrial fibrillation (%)	78 (21.6)
Heart disease (%)	45 (12.5)
Hypertension (%)	274 (75.9)

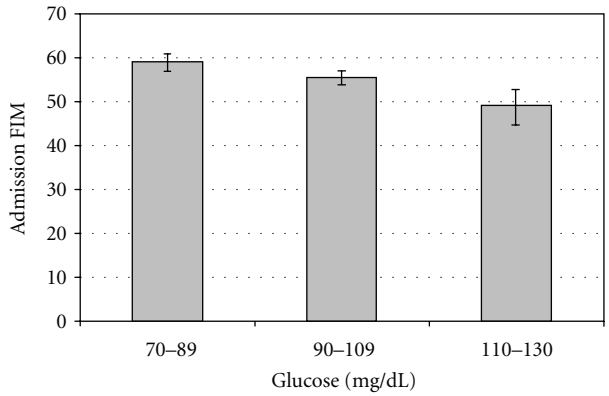

Figure 1: Admission FIM scores versus fasting glucose concentration. Lower admission FIM scores correspond to more severe strokes. Error bars are standard errors. The Mann-Whitney P value for the difference between lowest and highest glucose groups is 0.002. The P value for the slope of the glucose-admission FIM regression line is 0.003.

FBG was measured on average 9.4 days (median 7 days) after the acute stroke event.

Figure 1 shows the univariate relation between AFIM and FBG in the range 70–130 mg/dL. It appears from the figure that decreasing AFIM (increasing stroke severity) is associated with increasing FBG within the entire 70–130 mg/dL range (correlation coefficient −0.17; $P < 0.003$).

Table 2 shows correlates of AFIM in our multiple linear regression model. It appears that FBG significantly correlates with AFIM (partial correlation −0.165, CI −0.263 to −0.063, $P = 0.002$). To check that the glucose-AFIM relationship observed during multiple regression analysis was not due to chance interactions between dependent and independent variables, regression runs were conducted with different combinations of 3, 4, and 5 independent variables as well as 11 independent variables shown in Table 2. Regardless of the variables included, the FBG-AFIM relationship remained strong. For example, for regression including AFIM, age, gender, and FBG, the FBG-AFIM partial correlation coefficient was −0.176 ($P = 0.0008$); for regression including

Table 2: Variables associated with admission stroke severity (FIM) linear-regression model parameters*.

	Partial correlation	95% conf. limits		P value
Fasting blood glucose	−0.165	−0.263	−0.063	0.002
Age	−0.156	−0.254	−0.054	0.003
Gender	−0.108	−0.209	−0.006	0.043
Ethnic group	0.045	−0.058	0.147	0.403
BMI	0.156	0.054	0.254	0.003
Systolic blood pressure	0.031	−0.072	0.133	0.562
Temperature	−0.152	−0.251	−0.050	0.004
Days since stroke	−0.349	−0.436	−0.256	0.000
Atrial fibrillation	−0.012	−0.115	0.091	0.822
Heart disease	0.022	−0.081	0.124	0.687
Hypertension	0.025	−0.078	0.127	0.644

* Multiple R: 0.484167; R^2: 0.234417.

AFIM, age, systolic blood pressure, and temperature, the same partial correlation was −0.160 ($P = 0.002$); and for regression including AFIM, age, gender, body mass index, days since stroke, and FBG, corresponding results were −0.174 ($P = 0.001$).

When records for patients with blood glucose at the high end of the normal range (110–130 mg/dL) were compared to those at the low end (70 and 90 mg/dL), the odds ratio for more severe disability (below average AFIM score) was 2.02 (95% CI 1.10–3.73, $P = 0.022$). On average, there was a decrease of 0.25 FIM points for each mg/dL increase in blood glucose. Since a difference of four FIM points is considered clinically significant, each 16 mg/dL increment in blood glucose was thus associated with a clinically significant increase in impairment.

Analysis of different days-since-injury ranges (0–20, 5–25, . . . , 30–50) indicated that glucose levels did not change significantly. For 0–20 days since injury, average glucose changed only from 108.9 to 106.0 mg/dL.

4. Discussion

Our study shows that even in the normal range of FBG, there is a significant association between more severe strokes and higher FBG one week after the stroke. As blood glucose was measured at a time when the stress-induced BG increase [12, 19–21, 23] is known to have resolved [7, 23, 24], our study points to a graded association between higher glucose concentrations and more severe stroke-induced brain injury.

Most studies point to a direct association between stroke severity and BG concentrations at stroke onset [6–12]. In these studies, the association was investigated and observed only for BG in the hyperglycemic end of the BG spectrum while the relation between stroke severity and BG within the normal range of the spectrum has not been studied before. In the aforementioned studies, BG was measured on admission to hospital several hours after stroke onset but still within the first 24 hours of the stroke in the majority of cases. At that time, BG is elevated in response to the stroke incident [12, 19–21, 23]. Hence, BG measured at that time

point cannot be taken to reflect the patients habitual BG at stroke onset which is the more likely BG concentration prevailing in the time period shortly after the stroke where most irreversible brain damage takes place [16]. At one week after stroke, FBG concentrations have declined and have stabilized, and the FBG concentration may then reflect the patient's habitual BG concentration at the time of the stroke [22]. We consider this the most likely explanation for the strong association between stroke severity and FBG at one week after the stroke seen in our study.

It is well known that outcome in stroke patients undergoing thrombolytic therapy is poorer in patients who are hyperglycemic at the onset of treatment [11–13]. In the ECASS-II trial [12], BG was measured within 6 hours and repeated at 24 hours after the stroke. Whereas persistent hyperglycemia (at baseline and at 24 hours after stroke) was highly associated with poorer outcome, this was not seen in patients in whom hyperglycemia only was transient and present on the initial examination while not at the 24-hour examination. This observation may indicate that the unfavorable influence of hyperglycemia on outcome is seen only in the patients who are hyperglycemic already at stroke onset rather than those who experience transient hyperglycemia building up as a stress response in the hours after the stroke. This observation also supports the hypothesis that BG measured hours after stroke cannot be taken to reflect the BG concentration at the time of stroke onset which is more likely the BG concentration when most irreversible brain damage takes place.

There is compelling experimental and clinical evidence of an association between hyperglycemia and poorer outcome after stroke [6–13]. Our study now provides clinical evidence indicating that higher FBG concentrations even within the normoglycemic range are also associated with poorer outcome. This is in line with numerous animal studies showing a toxic effect of higher glucose concentrations in ischemic brain tissue in particular those demonstrating glucose as the substrate for lactate formation in the ischemic penumbra [1–5].

Due to encouraging results of treatment regimes using tight glucose control in management of critically ill patients [28–30], current guidelines recommend lowering of BG at least if high on admission [31]. However, attempts to replicate the findings of promising previous reports have recently failed, and concerns about safety have been raised as the risk of inducing potentially harmful hypoglycemia appears to be high in patients subjected to tight glucose control regimens [32, 33]. To date, the GIST-UK trial [20] is the only completed randomized study on glucose-lowering therapy in stroke. This trial sought to determine whether treatment with glucose-potassium-insulin infusion for 24 hours to maintain normoglycemia within the range of 70–130 mg/dL might reduce death or severe disability at 90 days after stroke. The result of this study was negative; the investigators did not find evidence of a beneficial effect of insulin treatment on death or disability after stroke, and concerns about safety were raised as a number of patients required rescue intravenous glucose treatment for hypoglycemic episodes. Treatment was, however, instituted a mean of 13 hours after the stroke at a time when most irreversible brain damage already had taken place. Hence, the negative outcome of the study does not preclude that higher BG at the time of stroke may augment brain damage and increase initial stroke severity. An alternate interpretation of this study is that glucose lowering therapy should be initiated very early after stroke onset (as is thrombolytic therapy).

A limitation to our study is the retrospective design and that we only included patients eligible for a stroke rehabilitation program. Therefore, patients in this study are in the moderate range of the stroke severity spectrum, while patients with very severe and mild strokes are relatively few. Also patients who died within the first week from stroke onset were not included in our data, and very old patients as well as previously severely handicapped patients may not have been referred for rehabilitation. Our study population is, however, large, and a multivariate analysis confirmed the FBG-stroke severity association with greater than 99% confidence. We therefore believe that our conclusions are not affected by selection bias to any significant degree. The fact that fasting blood glucose was measured at one week after stroke instead of at the time of acute hospital admission is considered an advantage of this study. We used a functional score to measure stroke severity. Although this is not a direct measure of the extent of the stroke lesion per se, functional stroke scores have been shown to correlate closely with lesion size [34]. We did not include patients with FBG >130 mg/dL and patients with diabetes in our study. First, because it is already amply demonstrated by others [6–13] that BG in nondiabetic patients with BG >130 mg/dL is directly associated with stroke severity, second a number of patients with BG >130 mg/dL may have prediabetes or unmasked diabetes, and third it is already well known that BG in patients with diabetes is not associated with stroke severity [7, 24].

In conclusion, our study provides clinical evidence of an association between more severe strokes and higher BG even within the normoglycemic range following stroke. The finding is, however, new and needs confirmation in other independent populations before entering into considerations of clinical implications.

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