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Glucose variability and mortality in patients with sepsis*

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Abstract

Objective—Treatment and prevention of hyperglycemia has been advocated for subjects with sepsis. Glucose variability, rather than the glucose level, has also been shown to be an important factor associated with in-hospital mortality, in general, critically ill patients. Our objective was to determine the association between glucose variability and hospital mortality in septic patients and the expression of glucose variability that best reflects this risk.

Design—Retrospective, single-center cohort study.

Setting—Academic, tertiary care hospital.

Patients—Adult subjects hospitalized for >1 day, with a diagnosis of sepsis were included.

Interventions—None.

Measurements—Glucose variability was calculated for all subjects as the average and standard deviation of glucose, the mean amplitude of glycemic excursions, and the glycemic lability index. Hospital mortality was the primary outcome variable. Logistic regression was used to determine the odds of hospital death in relation to measures of glucose variability after adjustment for important covariates.

Main results—Of the methods used to measure glucose variability, the glycemic lability index had the best discrimination for mortality (area under the curve = 0.67, $p < 0.001$). After adjustment for confounders, including the number of organ failures and the occurrence of hypoglycemia, there was a significant interaction between glycemic lability index and average glucose level, and the odds of hospital mortality. Higher glycemic lability index was not independently associated with mortality among subjects with average glucose levels above the median for the cohort. However, subjects with increased glycemic lability index, but lower average glucose values had almost five-fold increased odds of hospital mortality (odds ratio = 4.73, 95% confidence interval = 2.6 – 8.7) compared with those with lower glycemic lability index.

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Conclusions—Glucose variability is independently associated with hospital mortality in septic patients. Strategies to reduce glucose variability should be studied to determine whether they improve the outcomes of septic patients.

Keywords

sepsis; hyperglycemia; insulin therapy; mortality

Patients with sepsis, a manifestation of infection where systemic signs of inflammation are present and vital organ function may be impaired, are at greater risk of death than those suffering from uncomplicated infections (1). This syndrome accounts for >500,000 emergency department visits, 750,000 hospitalizations, and 215,000 deaths per year in the United States (2, 3). These patients are particularly prone to hyperglycemia and insulin resistance because of a number of pathophysiologic changes associated with sepsis (4 – 6).

Extreme elevations of blood glucose are associated with excess mortality in various groups of hospitalized patients (7–10). Targeting normoglycemia with the use of continuous insulin infusions (intensive insulin therapy [IIT]) improves outcomes in a selected group of critically ill patients (11, 12). In these single-center studies, patients who seem to derive the most benefit from IIT are patients recovering from surgery and those in the intensive care unit (ICU) >72 hrs. However, newer multicenter randomized studies of IIT in ICU patients, many of whom had sepsis, have yielded conflicting results. In one large multicenter study of general critically ill patients, treating to achieve a moderately hyperglycemic goal (140 –180 mg/dL) yielded similar survival with fewer hypoglycemic reactions compared with IIT (13). In a separate trial of patients with severe sepsis, IIT did not improve survival, but significantly increased the number of hypoglycemic events (14). The current recommendation from the Surviving Sepsis Campaign is that insulin therapy be used to maintain glucose below 150 mg/dL in septic patients (15).

One explanation for these mixed results is that measures of glucose control other than the glucose concentration may also be important. A recent study showed that glucose variability, manifest as the SD, was independently associated with hospital mortality in a mixed population of critically ill patients (16). Previous *in vitro* studies have shown that acute fluctuations of glucose can induce endothelial cell damage and apoptosis (17). This may represent a mechanism by which glucose variability confers worse outcomes. It has recently been proposed that in diabetic outpatients, glucose variability should be used as the gold standard of glycemic control (18). These observations, coupled with the lack of efficacy in recent studies of IIT in sepsis, led us to hypothesize that glucose variability might be associated with mortality in these patients. To test this, we analyzed the effect of glucose variability on hospital mortality for a cohort of septic patients.

MATERIALS AND METHODS

Subjects

We used a validated method (19) to identify hospital records with a discharge diagnosis (International Classification of Diseases version 9) consistent with sepsis. Subjects were included if they were admitted to The Ohio State University Medical Center during the 2005 calendar year. Subjects were excluded if they were <18 yrs, had a hospital length of stay of <24 hrs, or were incarcerated. Only the first hospitalization for any individual was included in the analysis. During the study period, there were general guidelines available recommending the avoidance of hyperglycemia, but these as well as nutrition and sepsis-specific care practices were not standardized by protocol.

Data Collection

All patient characteristics, resource use, outcomes data, glucose values, and management were collected from the electronic medical record. Comorbidities and organ failures were determined through validated methods (19, 20) using diagnosis and procedural codes contained in this electronic medical record.

All glucose values from testing in the central laboratory and all near-patient capillary tests for the entire hospitalization were included for this analysis. These glucose values were obtained from our electronic medical record and included date, time, and source of sample data. Mean glucose values for each patient were calculated using all glucose values for the admission. Three different expressions of glucose variability were explored: the glycemic lability index (GLI), mean amplitude of glycemic excursion, and SD. GLI is calculated as the squared difference between consecutive glucose measures per unit of actual time between those samples (21) ($GLI = \Sigma\{[\Delta\text{glucose (mmol/L)}]^2 \cdot \text{hr}^{-1}\} \cdot \text{wk}^{-1}$). Mean amplitude of glycemic excursion is defined as the mean of absolute values of any $[\Delta\text{glucose (consecutive values)}]$ that are > 1 SD of the entire set of glucose values (22). SD was calculated as the square-root of the average of the squared differences between individual glucose values and the mean.

Analysis

Because of exploratory work (see Results), we used GLI as the primary explanatory variable. Hospital mortality was the primary outcome. We explored potential confounders, including patient demographics (age, race, gender, and insurance status), comorbidities included in the Charlson-Deyo score (20), the number of organ-failures, hypoglycemia and process of care variables (ICU admission, insulin administration and frequency of glucose monitoring, and capillary testing). We identified a significant interaction ($p < 0.001$) between mean glucose and GLI. Although GLI was linear in the logit for hospital mortality, we dichotomized GLI at the median for the cohort to facilitate analysis and interpretation of the interaction. For consistency, mean patient glucose was similarly dichotomized at the cohort median.

We used logistic regression to estimate unadjusted odds of mortality including the interaction between GLI and mean patient glucose. A risk-factor approach was used to build the model for analysis of the primary outcome. Covariates were added individually and included in the final model as confounders if the odds ratios for either glucose variable (mean glucose or GLI) were changed by $>15\%$. Covariates in the final model were then checked for interactions with the glucose variables. None met our *a priori* level for inclusion ($p < 0.05$). Fractional polynomials were used to check that continuous variables were linear in the logit.

In descriptive analyses, we used analysis of variance or Kruskal-Wallis tests and chi-squared tests for continuous and categorical variables, respectively. We used the area under the receiver operating characteristic curve to compare the discrimination of mortality for various measures of glucose variability (23). All analyses were run using Stata 9.2 (Stata, College Station, TX). This study was approved by the Ohio State University Biomedical Institutional Review Board.

RESULTS

In 2005, there were 1,599 individual hospitalizations at Ohio State University Medical Center with a discharge diagnosis of sepsis and a length of hospitalization of at least one day. Figure 1 outlines subjects included and excluded from analysis. Ultimately, we analyzed data from 1,246 septic subjects (77.9% of initially identified records).

Determination of Glucose Variability

First, we explored the relationship between different expressions of glucose variability and hospital mortality. Using differences in the area under the receiver operating characteristic curve, the GLI had significantly better discrimination ($p < 0.001$) of in-hospital mortality than other measures of glucose variability (Table 1). Additionally, GLI also had the highest associated odds ratio of death per unit change across deciles of variability. Therefore, we used GLI for subsequent analyses of associations between glucose variability and outcome. Separately, hypoglycemia was associated with mortality in unadjusted analyses (if glucose was <60 mg/dL, odds ratio = 1.50, 95% confidence interval = 1.16–1.95, $p = 0.002$ or <40 mg/dL, odds ratio = 1.92, 95% confidence interval = 1.36–2.71, $p < 0.001$).

Cohort Characteristics

Because we found a significant interaction between the glucose-related measures, we divided subjects into four groups based on their GLI and mean glucose level, relative to the study cohort's median. Group I included subjects with GLI and average glucose below the cohort's median values (GLI = 27.4 and glucose = 133 mg/dL) and served as the reference group for all analyses. Group II included patients with average hospital glucose above and GLI below the cohort median. The remaining groups were defined as those with higher GLI and either lower (III) or higher (IV) than average glucose during their hospitalization.

There were no significant differences in race, gender, insurance status (not shown), or admission source between the four groups (I–IV) (Table 2). Both age and Charlson score were higher and the diagnosis of diabetes more common in groups II–IV than in the reference group (Table 2). Subjects with high GLI (III and IV) had glucose monitored more frequently, were treated more often with continuous intravenous insulin and more likely to experience hypoglycemic episodes (<60 mg/dL) during their hospitalization (Table 2). Subjects in the reference group (group I) had less organ failure, less frequent admission to the ICU, and lower hospital mortality than the other groups (Table 3).

Glucose Variability's Association with Mortality

When we divided the cohort into deciles of GLI, there was higher observed mortality with increasing levels of variability (Fig. 2). After adjustment for confounders including the number of organ failures, hypoglycemia, and the intensity of glucose testing and treatment, among subjects with an average glucose below 133 mg/dL (cohort median), increased variability was associated with significantly increased odds of hospital mortality (odds ratio = 4.73, 95% confidence interval = 2.6–8.7). Among patients with average glucose levels above the cohort median, those with higher variability had a nonsignificant increase in the odds of hospital mortality (odds ratio = 1.35, 95% confidence interval = 0.8–2.4). Patients with higher average glucose levels had an increase in their adjusted odds of death, but the effect was only significant among patients with lower GLI values (Table 4). The association of GLI and mortality remained even after adjusting for a diagnosis of diabetes in the final model. All together, it seemed that the effect of variability and average glucose was not additive, suggesting the importance of both variables.

DISCUSSION

We have demonstrated in a large cohort of septic patients that glucose variability is independently associated with increased hospital mortality. This effect was independent of hypoglycemia, the presence of diabetes, organ failures, glucose testing, and treatment. A particularly interesting observation was the dramatic increase in the odds of hospital mortality for patients with average glucose levels below the cohort median (<133 mg/dL). Considering that the current recommendation for treatment of hyperglycemia is well above

this level (150 mg/dL) (15), these patients may not be recognized as being at increased risk of death and therefore, not singled out for intervention.

Considerable data exist regarding the influence of cytokines, hormones, and the regulation of glucose transporters on hyperglycemia in sepsis (24, 25). However, it is less clear what factors are involved in greater glucose variability in patients without hyperglycemia. In our cohort, almost 10% of subjects had increased glucose variability without increased average glucose levels. Variability could be related to patient factors such as increased insulin resistance or treatment factors like the use of IIT. We are currently investigating this in our cohort. However, our data do not refute the idea that hyperglycemia itself is harmful. Sustained hyperglycemia likely has its own deleterious effects on inflammation and organ function (4, 24–26). In our report, these seem to represent separate manifestations of glucose risk that are not additive as no additional risk is apparent when both hyperglycemia and hypervariability occur together (Table 4).

Regardless of the mechanism, there are several ways in which high glucose variability could be harmful in patients with sepsis. Recent analyses of patients with insulin requiring diabetes mellitus suggest a link between glucose variability and end-organ damage through endothelial dysfunction (22, 26). One of these reports showed a significant association between variability of glucose and 8-iso-prostaglandin-F2 α , a marker of oxidative stress and potential mediator of organ dysfunction (26). This association was unaffected by traditional longer-term measures of glucose (mean glucose or Hemoglobin A1c). It is plausible that increased oxidative stress may play a role in poorer outcomes among septic patients.

Another mechanism that could mediate harm from high glucose variability is the occurrence of hypoglycemia. Some reports have shown an association between hypoglycemia and increased mortality among ICU patients (7, 27), whereas others have questioned this link (28, 29). In the recent GLUCONTROL trial, patients experiencing hypoglycemic episodes had higher mortality, independent of their severity of illness (13). Although hypoglycemia was associated with mortality in unadjusted assessments, our final mortality analysis shows that the risk of glucose variability is independent of hypoglycemia. This finding was consistent regardless of the threshold at which we defined hypoglycemia (<60 mg/dL or <40 mg/dL). Because glucose monitoring in critical care units is not continuous, our observed association between glucose variability and mortality could be explained by the occurrence of occult unmeasured hypoglycemia. This could be especially relevant in our cohort because sepsis has been noted to be a common condition in critically ill patients experiencing hypoglycemia (30, 31).

Our analysis has several limitations. Our sepsis cohort was defined using administrative data. However, this approach was previously validated as an alternative to manually screening medical charts (19). As a result, we cannot comment on the effects of the source of suspected infection or specific pathogen on glucose variability. Additionally as a result of the use of discharge information, we are unable to determine the timing of important events during the hospitalization. For example, we cannot establish the timing of organ failures with respect to either the onset of sepsis, glucose variability, or other unmeasured factors. Additionally, we were unable to use a physiology-based severity of illness score for risk-adjustment and we are missing information about other treatments these patients might have received. For example, the specific doses of insulin used to treat a glucose value might contribute to the variability of glucose control (32). Although standard insulin management algorithms were used in our hospital, we have no data to report how uniformly it was implemented. To address this limitation, we were able to adjust for the intensity of the insulin management strategy used for each patient in the analysis. Similarly, other treatments that affect glucose regulation, like the mode of administering steroids and

nutritional support practices, remain unmeasured. Finally, our use of capillary specimens could influence the observed variability of glucose as they may differ from whole blood measures (33). To address this in our final analysis, we adjusted the proportion of capillary tests used and found that the mortality relationship remained. Despite these limitations, our model fits the observed data extremely well (area under the curve, 0.830 and Hosmer-Lemeshow, $p = 0.25$), suggesting appropriate risk-adjustment.

We used all available glucose values during a subject's hospitalization, an approach that enhances our assessment of glucose variability. Of the tested measures of glucose variability, GLI seemed to best characterize the association with mortality ($p < 0.001$ compared with SD or mean amplitude of glycemic excursion). This may have been due to the inclusion of time and, therefore, rate of change in the calculation. GLI was originally developed to describe glucose variability in diabetic outpatients with testing 4 – 6 times per day (21). This rate of measurement mirrors our cohort where, on average, patients were tested 4.8 times per day. Studies which only include first-morning glucose measures (11, 12) may under-represent fluctuations in glucose. This limits the ability to compare the effects of glucose variability between these studies. It remains untested if measures of glucose variability, such as GLI, explain the discrepant results of recent IIT studies.

We are unaware of tested therapeutic approaches to reduce glucose variability in the critically ill. Insulin treatment regimens designed to specifically reduce variability, in addition to considering absolute glucose concentration, could be developed. It is possible that preventing wide swings in glucose might complement controlling glucose levels to within a specific range. Nutritional support is common among ICU patients and might affect glucose homeostasis (34, 35). Strategies to deliver consistent caloric supply, including agents that reduce glucose absorption, could reduce both hyperglycemia and glucose variability. These drugs have been successfully used to reduce end-organ complications in outpatients with impaired glucose tolerance (36). Finally, newer technologies which provide continuous glucose monitoring could lead to a better understanding of glucose variability and more timely treatment.

CONCLUSIONS

In summary, we have demonstrated in a large cohort of patients with sepsis that glucose variability is associated with hospital mortality independent of clinically-relevant factors. Glucose variability has been proposed as a new “gold-standard” for glycemic control in the outpatient management of diabetes mellitus (18). Our observation, if prospectively confirmed, would indicate that future approaches to glucose management in patients with sepsis should include glucose variability as a target for therapeutic intervention.

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Figure 1.

Cohort selection criteria. Patient records were selected from all inpatient records from 2005 based on discharge diagnoses. Numbers of subjects and reasons for exclusion are reported. The 21 subjects listed as having “limited glucose data” had only one value for glucose recorded during their hospitalization, thus making the calculation of variability impossible. *LOS*, length of stay.

Figure 2.

Observed mortality for the whole sepsis cohort by glucose measure. All hospital measures of glucose were used to generate glycemic lability index (*GLI*). From this the expected mortality was generated across the range of observed values of glucose. Each decile contains approximately 125 subjects.

Table 1

Comparison of the relationship between glucose variability and mortality in patients with a diagnosis of sepsis

Glucose Variability Term	Logistic Regression		Comparison of Mortality Discrimination		
	Mortality Crude Odds Ratio ^a	p	95% CI	Area Under the ROC	p ^b 95% CI
GLI	1.25	<0.001	1.20–1.32	0.67	0.64–0.71
MAGE	1.12	<0.001	1.07–1.18	0.59	<0.001 0.56–0.63
Standard deviation	1.16	<0.001	1.11–1.21	0.62	<0.001 0.58–0.65

GLI, glycemic lability index; MAGE, mean amplitude of glycemic excursions; ROC, receiver operating characteristic; CI, confidence interval.

For each subject in the entire cohort, the stated glucose variability term was calculated.

^a All logistic regression results are expressed as the increased odds of mortality for each change across deciles of the variable of interest. ROC curves for each variable were then constructed and the AUC presented;

^b Test of the equivalence of the area under the ROC curve compared with GLI area.

Table 2

Demographics and glucose data for the sepsis cohort by patient group

Characteristic	Total	GLI Below Cohort Median		GLI Above Cohort Median		p
		Group I (Average Glucose Below Cohort Median)	Group II (Average Glucose Above Cohort Median)	Group III (Average Glucose Below Cohort Median)	Group IV (Average Glucose Above Cohort Median)	
N (%)	1,246	499 (40.0)	124 (9.9)	117 (9.5)	506 (40.6)	
Age (mean)	60.5	57.4	62.7	58.9	63.4	<0.001
Male (%)	52.7	53.9	58.1	49.6	51.4	0.472
Race (%)						0.691
White	66.2	65.5	68.6	61.5	66.8	
African-American	29.2	30.7	25.8	34.2	28.1	
Other	4.6	3.8	5.6	4.3	5.1	
Admission source (%)						0.135
ED	35.3	39.9	37.1	32.5	31.2	
Hospital transfer	33.8	30.4	30.6	36.7	36.6	
Diabetes (%)	31.8	9.4	19.4	36.8	56.5	<0.001
Charlson score, median (IQR)	2 (1-3)	1 (0-3)	2 (1-3.5)	2 (1-3)	2 (1-3)	<0.001 ^a
Mean glucose (±SD)	143 (41)	111 (13)	155 (21)	117 (13)	177 (37)	<0.001
Glucose variability [GLI, median (IQR)]	27.4 (2-134)	1.6 (0.5-5.6)	8.1 (2.7-16)	77 (45-157)	152 (73-332)	<0.001 ^a
Glucose measures per day, mean (±SD)	4.8 (5.1)	2.1 (2.0)	3.0 (3.0)	5.5 (3.4)	7.8 (6.3)	<0.001 ^a
Continuous IV insulin treatment (%)	25.7	7.0	10.5	28.2	48.0	<0.001
Hypoglycemia (%)	31.4	13.2	6.5	65.0	48.4	<0.001

ED, emergency department; GLI, glycemic lability index; IQR, interquartile range; IV, intravenous.

Unless otherwise stated, comparisons of proportion were analyzed with χ^2 analysis and means with the two-sample *t*-test. Hypoglycemia was defined as any glucose value <60 mg/dL. Population median for GLI, 27.4; population median for average hospital glucose, 133 mg/dL.

^a *p* value from Kruskal-Wallis test.

Table 3

Sepsis and outcome data for the cohort by patient group

Characteristic	Total	GLI Below Cohort Median		GLI Above Cohort Median		p
		Group I (Average Glucose Below Cohort Median)	Group II (Average Glucose Above Cohort Median)	Group III (Average Glucose Below Cohort Median)	Group IV (Average Glucose Above Cohort Median)	
Sepsis-associated organ failure (%)						
Respiratory	32.3	22.6	34.7	39.3	39.9	<0.001
Cardiovascular	15.5	11.8	11.3	19.7	19.0	0.004
Renal	54.8	42.7	43.5	65.8	68.0	<0.001
Hepatic	8.3	4.2	8.1	15.4	10.7	<0.001
Hematologic	24.0	21.8	22.6	29.1	25.9	0.264
Metabolic	21.5	16.0	23.4	29.9	24.7	0.001
Neurologic	7.4	7.0	11.3	11.1	6.1	0.096
Organ failure No. (%)						
0	25.0	34.7	33.0	15.4	14.8	<0.001
1	28.8	30.3	21.8	23.9	30.4	
2	19.3	18.0	15.3	25.6	20.2	
3+	26.9	17.0	29.8	35.0	34.6	
Hospital LOS, mean (±SD)	17.7 (21.3)	15.6 (18.2)	13.0 (14.0)	17.6 (18.8)	21.1 (25.3)	<0.001 ^a
ICU admit (%)	62.9	51.9	66.1	65.8	73.1	<0.001
ICU LOS, mean (±SD)	12.8 (17.7)	10.0 (13.2)	9.7 (13.0)	13.7 (18.6)	15.3 (20.6)	<0.001 ^a
Mortality (%)	27.6	13.2	39.5	35.9	36.4	<0.001

ICU, intensive care unit; LOS, length of stay; GLI, glycemic lability index.

p value represents the significance of changes across the four descriptive groups. (Population median for GLI 27.4; population median for average hospital glucose, 133 mg/dL.)

^a p value is based on natural log transformation.

Table 4

Adjusted odds ratios for hospital mortality for increased glucose variability and glucose concentration

Risk Factor	Patient Group	
	Average Glucose Below Cohort Median	Average Glucose Above Cohort Median
GLI above cohort median	4.73 (2.6–8.7)	1.35 (0.8–2.4)
	GLI Below Cohort Median	GLI Above Cohort Median
Average glucose above cohort median	5.48 (3.2–9.4)	1.57 (0.9–2.6)

A significant interaction between average hospital glucose and GLI was detected ($p < 0.001$) so all groups' odds of death are reported according to the presence of the first risk factor (glucose or GLI) in two patient groups divided by the presence or absence of the second risk factor. All reported odds ratio (with 95% confidence interval) are adjusted for significant covariates (Significant covariates included were the occurrence of hypoglycemia [<60 mg/dL], the presence of diabetes or renal failure, type of insulin treatment [continuous, intermittent, or none], proportion of capillary tests used, and number of organ failures [0, 1, 2, or 3+]) and refer to the adjusted odds of hospital death for subjects with the indicated risk factor relative to the group of patients without that risk factor.

The cohort median for GLI was 27.4 and for glucose was 133 mg/dL. Hosmer-Lemeshow goodness-of-fit p value = 0.247, model discrimination area under the receiver operating characteristic curve = 0.830; GLI, glycemic lability index.