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Glucometrics in Patients Hospitalized With Acute Myocardial Infarction

Defining the Optimal Outcomes-Based Measure of Risk

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Background—Hyperglycemia on admission is associated with an increased mortality rate in patients with acute myocardial infarction. Whether metrics that incorporate multiple glucose assessments during acute myocardial infarction hospitalization are better predictors of mortality than admission glucose alone is not well defined.

Methods and Results—We evaluated 16 871 acute myocardial infarction patients hospitalized from January 2000 to December 2005. Using logistic regression models and C indexes, 3 metrics of glucose control (mean glucose, time-averaged glucose, hyperglycemic index), each evaluated over 3 time windows (first 24 hours, 48 hours, entire hospitalization), were compared with admission glucose for their ability to discriminate hospitalization survivors from nonsurvivors. Models were then used to evaluate the relationship between mean glucose and in-hospital mortality. All average glucose metrics performed better than admission glucose. The ability of models to predict mortality improved as the time window increased (C indexes for admission, mean 24 hours, 48 hours, and hospitalization glucose were 0.62, 0.64, 0.66, 0.70; $P<0.0001$). Statistically significant but small differences in C indexes of mean glucose, time-averaged glucose, and hyperglycemic index were seen. Mortality rates increased with each 10-mg/dL rise in mean glucose ≥120 mg/dL (odds ratio, 1.8; $P=0.003$ for glucose 120 to <130 mg/dL) and with incremental decline <70 mg/dL (odds ratio, 6.4; $P=0.01$ versus glucose 100 to <110 mg/dL). The slope of these relationships was steeper in patients without diabetes.

Conclusions—Measures of persistent hyperglycemia during acute myocardial infarction are better predictors of mortality than admission glucose. Mean hospitalization glucose appears to be the most practical metric of hyperglycemia-associated risk. A J-shaped relationship exists between average glucose and mortality, with both persistent hyperglycemia and hypoglycemia associated with adverse prognosis. (***Circulation*. 2008;117:1018-1027.**)

Key Words: diabetes mellitus ■ glucose ■ myocardial infarction ■ prognosis

Previous studies have established that elevated glucose at the time of hospital admission is associated with increased mortality rates among patients hospitalized with acute myocardial infarction (AMI).[1–25] However, the admission glucose represents only a single measurement in time and does not reflect the overall exposure to hyperglycemia during the AMI hospitalization. An important unanswered question is whether persistent hyperglycemia during hospitalization has a greater impact on adverse outcomes in AMI than a single, random glucose measure. If it does, a second key question is how best to measure persistent hyperglycemia during AMI hospitalization. Although hemoglobin A_{1c} is a useful tool for assessing average glucose control in the outpatient setting, it has little prognostic value during acute AMI hospitalization.[19,26] Several candidate measures exist,[27–29] but no prior study has systematically evaluated their association with outcomes in AMI.

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To address these gaps in knowledge, we analyzed data from Cerner Corporation's Health Facts database, a national, contemporary database of patients hospitalized with AMI in 40 hospitals across the United States from 2000 to 2005. This database provided a unique opportunity to define the relationship between measures of persistent hyperglycemia and

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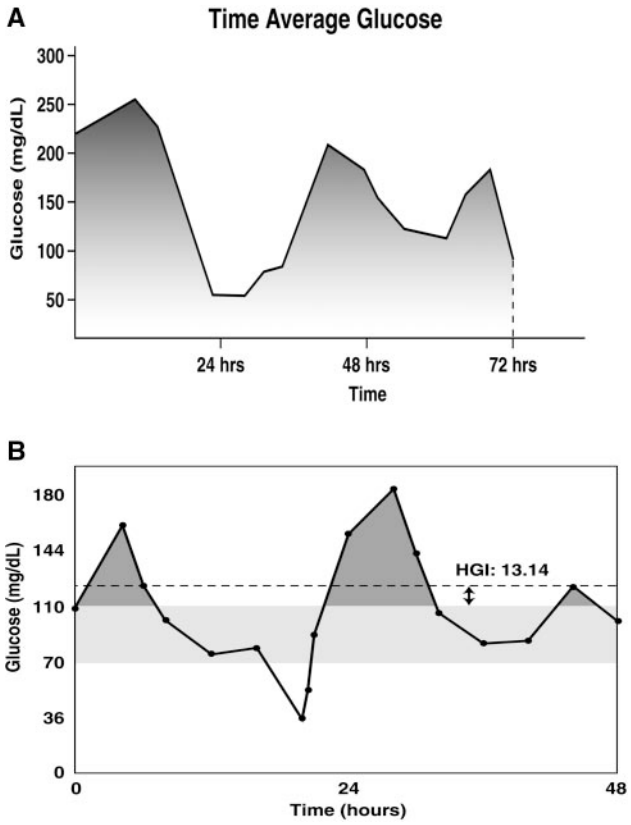

Figure 1. A, TAG (shaded area under the curve). B, HGI. All glucose values and corresponding measurement times are recorded; HGI is then calculated as the area under the glucose curve for hyperglycemic values only (shaded areas under the curve) divided by the length of observation period. In this example, HGI is 13.14 mg/dL. Adapted from Vogelzang et al. *Crit Care*. 2004;8:R122–R127; originally published by BioMed Central Ltd. and accessible online at http://ccforum.com/content/8/3/R122.

outcomes after AMI through the use of detailed information regarding glucose measurements in a large, unselected group of patients. We sought to identify the summary metric of persistently elevated glucose during hospitalization with the greatest association with inpatient mortality and to establish whether this metric is a superior predictor of prognosis than admission hyperglycemia alone.

Methods

Data Source

The data source for this study was the Cerner Corporation's Health Facts database. All 40 participating medical centers in the Health Facts consortium contributed deidentified information on consecutive patients treated between January 1, 2000, and December 31, 2005. Data included demographics, medical history, comorbidities (determined from the *International Classification of Diseases*, ninth edition, clinical modification [ICD-9-CM] diagnostic codes), comprehensive laboratory data (including all venous and fingerstick blood glucose measurements during hospitalization), comprehensive pharmacy data, in-hospital procedures (including cardiac catheterization, percutaneous coronary intervention, coronary artery bypass surgery), in-hospital mortality, and hospital characteristics (eg, geographic region, number of beds, presence of cardiac catheterization and angioplasty facilities, presence of cardiothoracic surgery facilities, and teaching versus nonteaching status).

Table 1. Matrix of Glucose Metric–Time Window Combinations Evaluated

	Glucose Metric			
Time Window	Single Value	Mean	TAG	HGI
Admission	X			
First 24 h		X	X	X
First 48 h		X	X	X
Entire hospitalization		X	X	X

Study Cohort

We identified all patients hospitalized with the primary discharge diagnosis of AMI between January 2000 and December 2005 (using ICD-9-CM codes 410.xx and excluding 410.x2, which represents readmission after AMI) who had at least 1 glucose measurement during the first 24 hours after admission and at least 1 documented abnormal troponin I or T or creatine kinase-MB fraction (n=23 613). Subsequently, those patients who were transferred from or to other acute care facilities were excluded (n=6742) because complete laboratory and medication administration details for patients' entire episode of AMI care were not available. Our final study cohort included 16 871 patients hospitalized with biomarker-confirmed AMI.

Inpatient Glucose Assessment

The Health Facts database provided access to all of the patients' glucose values (both capillary and plasma assessments), including the time of measurement for each value. All of the patients' plasma glucose values were analyzed. Whole-blood glucose specimens were converted by glucose meters into plasma glucose values (in units of milligrams per deciliter) for all analyses (plasma glucose equals whole-blood glucose times 1.15).

Candidate Glucose Metrics

A principal objective of this study was to identify the most prognostically important measure of hyperglycemia during AMI. This involved defining alternative metrics and comparing them with admission glucose alone, the most commonly used current measure. Several candidate summary measures of glucose control over time were considered, including mean glucose,[27,28] time-averaged glucose (TAG), and the hyperglycemic index (HGI).[29]

Mean glucose is a simple average of each patient's glucose levels over time. TAG is derived as the area under the curve of all glucose values during a specified time period divided by the length of that observation period (Figure 1A). HGI, calculated according to the methodology of Vogelzang et al,[29] accounts only for the area under the curve of hyperglycemic glucose values over the length of stay, ignoring hypoglycemia (Figure 1B).

To determine whether the prognostic impact of these metrics is time dependent, each of these measures (except admission glucose) was evaluated over different time windows during AMI hospitalization: the first 24 hours, the first 48 hours, and the entire length of hospitalization. Overall, 10 different glucose metric–time window combinations were evaluated, as detailed in Table 1. All of the metrics were analyzed both as categorical variables (similar to previously published cut points)[1] and as continuous variables.

Diabetes Definition

Given previous reports that the nature of the association between elevated glucose and outcomes differs in patients with and without diabetes, stratified analyses were performed. Patients were classified as having recognized diabetes if they had a corresponding ICD-9-CM code or were treated with an oral antihyperglycemic agent or any extended-release insulin during hospitalization.

Outcomes

The outcome for this study was all-cause in-hospital mortality as obtained directly from the Cerner Health Facts database.

Table 2. Baseline Characteristics of Patients Within Different Mean Hospitalization Glucose Subgroups

	Mean Hospitalization Glucose, mg/dL					
	<110 (n=3901)	110–<140 (n=6014)	140–<170 (n=3040)	170–<200 (n=1589)	≥200 (n=2327)	*P*
Demographic characteristics						
Age, y	68.4±15.7	69.3±14.2	71.6±13.0	70.7±12.4	69.3±13.3	<0.001
Race (white), %	87.9	89.4	88.6	87.5	87.0	<0.001
Female, %	42.7	40.7	43.7	45.2	50.4	<0.001
Clinical characteristics, %						
Heart failure	25.9	31.5	43.2	45.9	48.6	<0.001
Hypertension	51.3	51.8	52.0	53.6	50.7	0.446
Stroke	4.1	4.0	4.3	4.1	4.2	0.965
PVD	5.3	5.4	5.4	5.3	5.3	0.998
Dementia	3.0	2.2	2.4	1.7	2.6	0.022
COPD	11.3	11.4	11.6	12.6	10.7	0.506
Diabetes	6.4	13.7	37.0	60.0	75.8	<0.001
In-hospital procedures, %						
Coronary angiography	50.5	51.8	45.7	45.6	39.2	<0.001
PCI	31.9	32.6	24.6	23.2	19.6	<0.001
CABG	1.9	8.3	12.6	13.2	7.6	<0.001
Admission laboratory values						
Creatinine, mg/dL	1.3±1.1	1.3±1.0	1.5±1.1	1.5±1.0	1.6±1.3	<0.001
WBC count, 10^3/uL	9.6±4.1	10.7±6.4	11.3±6.1	11.6±5.1	12.4±7.5	<0.001
Hematocrit, %	37.0±11.1	38.0±10.1	37.7±9.8	37.2±9.9	37.4±9.4	<0.001
Peak troponin, ng/mL	37.0±76.0	61.2±123.6	61.6±184.3	63.8±145.2	58.0±124.8	<0.001
Length of stay, h	120.2±95.7	145.2±148.3	164.4±159.0	173.4±164.5	147.8±151.5	<0.001
In-hospital medications, %						
Aspirin	84.7	85.0	81.3	78.2	80.1	<0.001
Other platelet inhibitors	53.3	54.6	46.0	46.0	44.8	<0.001
β-Blocker	85.0	85.7	83.4	83.1	77.4	<0.001
Calcium channel blocker	19.5	22.4	25.7	26.1	26.0	<0.001
Diuretics	35.2	45.5	58.5	61.4	58.4	<0.001
Nitrates	76.2	81.1	81.1	80.1	78.4	<0.001
β-Adrenergic bronchodilators	10.3	16.3	22.8	22.8	24.5	<0.001
ACE/ARB	55.3	61.9	63.5	63.8	60.9	<0.001
Statins	55.3	58.5	55.0	55.8	52.7	<0.001
Oral antihyperglycemic agents	1.1	2.3	6.8	11.8	12.8	<0.001

PVD indicates peripheral vascular disease; COPD, chronic obstructive pulmonary disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; WBC, white blood cell; and ACE/ARB, angiotensin-converting enzyme/angiotensin receptor blocker.

Statistical Analysis

Baseline Characteristics

To compare baseline characteristics between patients with various degrees of hyperglycemia, patients were stratified into 5 groups according to their mean glucose during the entire hospitalization using mean hospitalization glucose levels of <110, 110 to <140, 140 to <170, 170 to 200, and >200 mg/dL. Baseline demographic and clinical characteristics were compared across the 5 glucose groups by use of Pearson's χ^2 test for categorical variables and ANOVA for continuous variables.

Comparison of the Glucose Metrics

Multiple logistic regression models were then constructed, with each glucose metric–time window combination as the independent variable and in-hospital mortality as the outcome. The prognostic power of the various glucose metrics was estimated using C indexes.[30] Separate C indexes were obtained for each of the glucose measure–time window combinations shown in Table 1. C indexes between models were compared using *U* statistics to test which glucose metrics and windows have the greatest prognostic value.[31] In addition, we compared model fit across the different glucose metric–time window combinations using Akaike's information criterion.[32] This approach was independently replicated for patients with and without diabetes.

Sensitivity Analysis

It is possible that glucose values may "naturally" decline during AMI hospitalization among survivors as the severity of illness decreases. If that were the case, then patients who die early would not have survived long enough to experience this natural reduction in their glucose levels. As a consequence, metrics of average glucose control

Table 3. Unadjusted Associations Between Glucose Metrics and In-Hospital Mortality

Glucose Metrics	All Patients		
	Died, n	Survived, n	Mortality Rate, %
Admission glucose, mg/dL			
<110	166	3204	4.93
110–<140	256	4592	5.28
140–<170	230	2629	8.04
170–<200	140	1491	8.58
≥200	539	3624	12.95
P			<0.001
24-h Mean glucose, mg/dL			
<110	145	3243	4.28
110–<140	273	5051	5.13
140–<170	244	2758	8.13
170–<200	167	1527	9.86
≥200	502	2961	14.50
P			<0.001
48-h Mean glucose, mg/dL			
<110	143	3442	3.99
110–<140	283	5406	4.97
140–<170	262	2717	8.79
170–<200	189	1523	11.04
≥200	454	2452	15.62
P			<0.001
Hospitalization mean glucose, mg/dL			
<110	113	3788	2.90
110–<140	293	5721	4.87
140–<170	296	2744	9.74
170–<200	187	1402	11.77
≥200	442	1885	18.99
P			<0.001
24-h TAG, mg/dL			
<110	142	3272	4.16
110–<140	278	5060	5.21
140–<170	247	2748	8.25
170–<200	161	1512	9.62
≥200	503	2948	14.58
P			<0.001
48-h TAG			
<110	145	3687	3.78
110–<140	295	5388	5.19
140–<170	266	2680	9.03
170–<200	194	1454	11.77
≥200	431	2331	15.60
P			<0.001
Hospitalization TAG, mg/dL			
<110	122	4326	2.74
110–<140	332	5722	5.48
140–<170	279	2511	10.00
170–<200	194	1337	12.67
≥200	404	1644	19.73
P			<0.001
24-h HGI			
0	103	2557	3.87
0–<30	313	5725	5.18
30–<60	249	2786	8.20
60–<90	161	1520	9.58
≥90	505	2952	14.61
P			<0.001
48-h HGI			
0	75	2182	3.32
0–<30	357	6796	4.99
30–<60	272	2755	8.99
60–<90	192	1471	11.55
≥90	435	2336	15.70
P			<0.001
Hospitalization HGI			
0	55	1748	3.05
0–<30	382	8138	4.48
30–<60	288	2616	9.92
60–<90	201	1377	12.74
≥90	405	1661	19.60
P			<0.001

during the entire hospitalization may appear to be better predictors of death simply because of this "survivor bias" rather than their inherent superior prognostic value.

To address this issue, we conducted a sensitivity analysis to eliminate a potential survivor bias. In this analysis, all metrics of average glucose control were recalculated after the exclusion of patients who died within each respective time window (Mean 24-hour glucose was recalculated after the exclusion of patients who died within the first 24 hours; mean 48-hour glucose, after the exclusion of patients who died during the first 48 hours; and mean hospitalization glucose, after the exclusion of patients who died during the first 72 hours). C indexes measuring the ability of each metric–time window combination to predict subsequent in-hospital mortality (death after the first 24 hours for the 24-hour metrics, etc) were then recalculated. The C index of each metric–time window combination was then compared with that of admission glucose.

Determining the Nature of the Relationship Between Persistent Hyperglycemia and Mortality

After the optimal glucose metric–time window combination was identified, multivariable logistic regression models were subsequently constructed to assess whether the association between this glucose metric and in-hospital mortality was independent of other patient factors. The chosen glucose metric was modeled as both a categorical variable (using the 5 glucose categories stated above) and

Table 4. C Statistics for Glucose Metric–Time Window Combinations (All Patients)

Time Window	Glucose Metric				*P* for Overall Comparison Across Metrics
	Admission	Mean	TAG	HGI	
Admission	0.619	N/A	N/A	N/A	N/A
24 h	N/A	0.643	0.643	0.647	0.0001
48 h	N/A	0.659	0.658	0.664	<0.0001
Hospitalization	N/A	0.700	0.704	0.708	0.0002
P for overall comparison across time windows		<0.0001	<0.0001	<0.0001	

a continuous variable (increments of 10 mg/dL). Patient characteristics previously demonstrated to be prognostically important and those identified in bivariate analyses as predictors of in-hospital mortality were entered into the models. Covariates included demographic factors (age, gender, race), comorbidities (heart failure, hypertension, cerebrovascular disease, peripheral vascular disease, chronic obstructive pulmonary disease, dementia), laboratory values on admission (creatinine, white blood cell count, hematocrit), peak troponin or creatine kinase-MB value, procedures during hospitalization (cardiac catheterization, percutaneous intervention, coronary artery bypass grafting), and medications during hospitalization (aspirin, clopidogrel, ticlopidine, β-blockers, calcium channel blockers, nitrates, diuretics, bronchodilators, HGM-CoA inhibitors). In addition, models were adjusted for the frequency of glucose testing because the intensity of testing could be related to both severity of hyperglycemia and in-hospital mortality. All models also adjusted for hospital length of stay and for clustering by site. Analyses were repeated within subgroups of patients with and without previously recognized diabetes. Nonlinear trends for all continuous variables were tested through the use of restricted cubic splines.

Analyses were conducted with SAS 8.02 (SAS Institute Inc, Cary, NC). Use of the Health Facts database was approved by the Saint Luke's Mid America Heart Institute's Institutional Review Board.

Role of the Funding Source

Cerner Corporation played a key role in the collection of the Health Facts data and approved the work submitted for publication. It did not have a role in the study design, data analysis, data interpretation, or writing of the manuscript.

The authors of the study had complete and unrestricted access to the data at all times and take responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Baseline Characteristics

Baseline characteristics of 16 871 patients across different mean hospitalization glucose groups are detailed in Table 2. Twenty-nine percent of the patient cohort had preexisting diabetes. The median number of glucose measurements per patient during hospitalization was 4 (interquartile range, 2 to 8). The average (mean) number of glucose measurements per patient was 7.8. More than 70% of the patients had ≥3 glucose measurements, and close to 60% of patients had ≥4 glucose measurements during their hospital stay. Compared with patients who had lower mean hospitalization glucose, greater proportions of those with higher mean glucose were female and had heart failure and diabetes. These patients also had higher presenting creatinine, white blood cell count, and peak troponin levels; were less likely to receive coronary angiography and percutaneous intervention; and were treated less frequently with aspirin and β-blockers and more frequently with diuretics and angiotensin-converting enzyme inhibitors. Patients in the lowest and highest glucose groups had the shortest lengths of stay.

Comparison of the Glucose Metrics

In unadjusted analyses, higher glucose values were strongly associated with increased risk of in-hospital mortality for all glucose metrics (Table 3). C indexes for all 9 alternative metrics of persistent hyperglycemia were significantly higher than that of admission hyperglycemia (Table 4). We also noted a gradual, statistically significant increase in the prognostic importance of glucose metrics as the time window increased so that the C index for any summary measure over the entire hospitalization was higher than the C indexes for glucose metrics over 48 and 24 hours. Although the differences between the C indexes for mean glucose, TAG, and HGI were statistically significant, they were small compared with the differences between all of the summary measures and the admission glucose value. The goodness-of-fit analysis using Akaike's information criterion showed very similar results; the goodness of fit of the models improved incrementally as the models progressed from admission glucose to 24-hour, 48-hour, and entire hospitalization metrics (Figure 2).

Similar results were seen within the subgroups of patients with and without recognized diabetes (data not shown). With the combination of statistical criteria and ease of calculation and clinical implementation, mean glucose during the entire hospitalization was selected as the most practical summary metric of glucose-associated risk.

Sensitivity Analysis

Accounting for possible survivor bias did not change the results. All metrics of average glucose control continued to be superior to admission glucose alone in their ability to predict in-hospital mortality (C indexes for patients who survived 24 hours: admission glucose, 0.616; 24-hour mean glucose, 0.637; TAG, 0.639; HGI, 0.643; $P<0.001$; C indexes for patients who survived 48 hours: admission glucose, 0.613; 48-hour mean glucose, 0.647; TAG, 0.642; HGI, 0.647; $P<0.001$; C indexes for patients who survived 72 hours: admission glucose, 0.613; hospitalization mean glucose, 0.691; TAG, 0.684; HGI, 0.692; $P<0.001$).

Nature of the Relationship Between Mean Hospitalization Glucose and In-Hospital Mortality

In unadjusted analysis, higher mean hospitalization glucose was strongly associated with higher in-hospital mortality (Table 3). When mean hospitalization glucose was analyzed

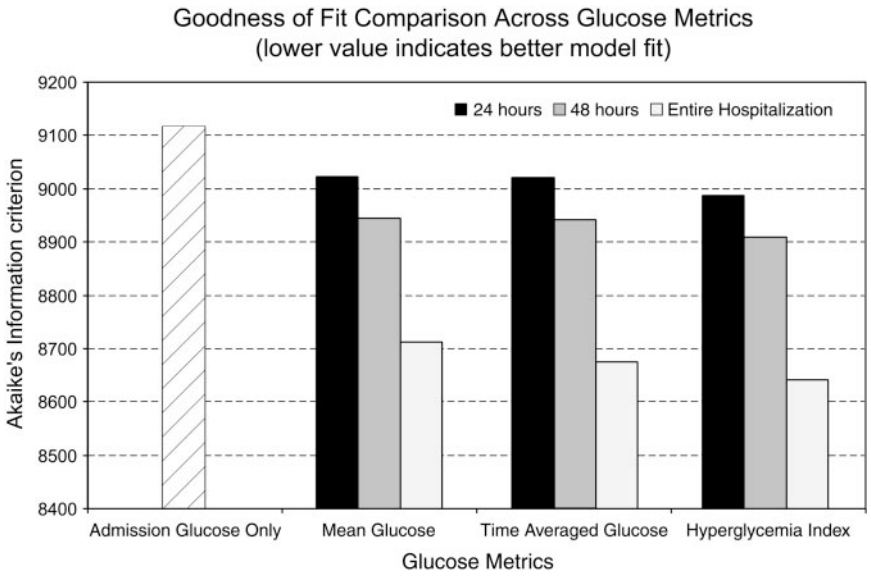

Figure 2. Comparison of goodness of fit across various glucose metric-time window combinations (using Akaike's information criterion; lower values indicate the preferred model).

in increments of 10 mg/dL, there was a clear J-shaped relationship between glucose values and mortality rates (Figure 3). There was a gradual increase in hospital mortality rate with each 10-mg/dL incremental rise in mean hospitalization glucose levels above a threshold of 120 mg/dL. The mortality rate also was higher in patients with low mean glucose levels, particularly those with glucose <70 mg/dL. The nature of the relationship also was J-shaped but different within the subgroups of patients with and without preexisting diabetes. Although in the normal glucose range patients without recognized diabetes had a lower mortality rate than patients with diabetes, their risk increased much more steeply at higher glucose levels, surpassing the risk of patients with diabetes at ≈130 mg/dL (Figure 3, *P* for diabetes–by–mean glucose interaction <0.0001).

After multivariable adjustment, the nature of these relationships persisted. Higher mean hospitalization glucose continued to be strongly associated with higher in-hospital mortality (Table 5 and Figure 4). There was a statistically significant, gradual increase in the odds of in-hospital mortality with each 10-mg/dL incremental rise in mean hospitalization glucose levels above the threshold of 120 mg/dL (eg, the odds ratio [OR] for patients with mean glucose of 120 to <130 mg/dL was 1.8, $P=0.003$, versus patients with a mean glucose of 100 to <110 mg/dL). The odds of death also were significantly higher in patients with glucose levels <70 mg/dL (OR, 6.4; $P=0.01$) compared with those who had mean glucose levels between 100 and <110 mg/dL. The odds of death associated with higher mean glucose rose steeply in patients without recognized diabetes once mean glucose levels exceeded 120 mg/dL. However, among patients with known diabetes, the curve was much less steep (Figure 4; *P* for diabetes–by–mean glucose interaction <0.0001); in fact, only those diabetic patients with severe, sustained hyperglycemia (mean hospitalization glucose >200 mg/dL) had significantly higher risk of death compared with those whose mean glucose levels were <110 mg/dL (Table 5).

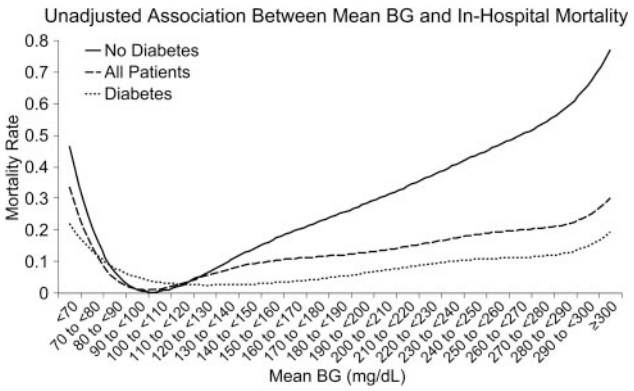

Figure 3. Nature of the relationship between mean hospitalization glucose and in-hospital mortality (unadjusted analysis). BG indicates blood glucose.

Discussion

In this large, contemporary cohort of patients hospitalized with AMI, we demonstrate that persistent hyperglycemia is a more important predictor of in-hospital mortality than admission hyperglycemia alone. There does not appear to be a specific critical period of vulnerability to hyperglycemia; ie, the adverse prognostic impact of elevated glucose extends and is compounded throughout the entire hospitalization, not just during the initial phase of hospitalization. Specifically, summary measures of average glucose control at any time point during hospitalization offer a significant, incremental advantage in their ability to predict mortality compared with admission glucose. Moreover, metrics that incorporate glucose values over longer time periods are prognostically superior to those that use the data from only the first 24 or 48 hours of hospitalization. Although more sophisticated measures of glucose control (such as HGI) had the highest discriminating ability in predicting mortality, the differences between HGI and the simple mean were relatively small compared with the differences between all of the summary measures and admission glucose. Given the ease of clinical implementation and calculation, mean glucose appears to be the most practical summary measure of glucose control in the

Table 5. Relationship Between Mean Hospitalization Glucose and In-Hospital Mortality After Multivariable Adjustment

Mean Hospitalization Glucose, mg/dL	All Patients		Patients With Diabetes		Patients Without Diabetes	
	OR	95% CI	OR	95% CI	OR	95% CI
<110	Referent		Referent		Referent	
110 to <140	2.00	1.55–2.58	0.96	0.39–2.38	2.14	1.65–2.78
140 to <170	3.56	2.75–4.63	1.27	0.54–3.01	4.70	3.57–6.21
170 to <200	4.74	3.55–6.33	1.57	0.65–3.76	8.13	5.88–11.24
≥200	7.81	6.06–10.10	4.10	1.81–9.26	15.39	11.24–21.28

setting of AMI. Mean hospitalization glucose also is a powerful predictor of in-hospital mortality independent of other demographic and clinical patient factors and potential confounders.

Our findings substantially expand current knowledge on the relationship between various metrics of glucose control and outcomes in patients hospitalized with AMI. Although hemoglobin A_{1c} has proved to be an important metric of average glucose control in the outpatient setting, it is not prognostically useful during hospitalization.[19,26] Given the many inherent challenges of glucose measurements during AMI hospitalization (variability of testing frequency among patients, samples obtained from different access sites and under various nutritional conditions, etc), a practically useful summary measure of glucose control in this setting has been needed. Although most prior studies have focused on the association between elevated glucose on admission and adverse events in AMI patients,[1–21,23,25] only a few have assessed the relationship between in-hospital hyperglycemia and mortality rates. Suleiman and colleagues[24] found that fasting glucose after admission for AMI was a more important predictor of 30-day mortality than admission glucose alone. Svensson et al[22] demonstrated that in diabetic patients with AMI, those with lowest whole-blood glucose ≥120 mg/dL during hospitalization had a 48% increase in the hazard of 2-year mortality compared with patients whose lowest hospitalization glucose was between 56 and 119 mg/dL. However, both of these studies used glucose values that were based on single measurements and thus were not indicative of patients' overall hyperglycemic exposure. Recently, a relatively small study of 417 patients with ST-elevation AMI demonstrated that TAG over the first 48 hours was a better discriminator of 30-day mortality than admission glucose alone.[33] However, mainly because of sample size and data limitations, prior studies have been unable to compare multiple glucose metric–time window combinations to define the best summary measure of glucose control during AMI hospitalization. No prior work has determined the nature of the relationship between persistent hyperglycemia and mortality rates in AMI patients.

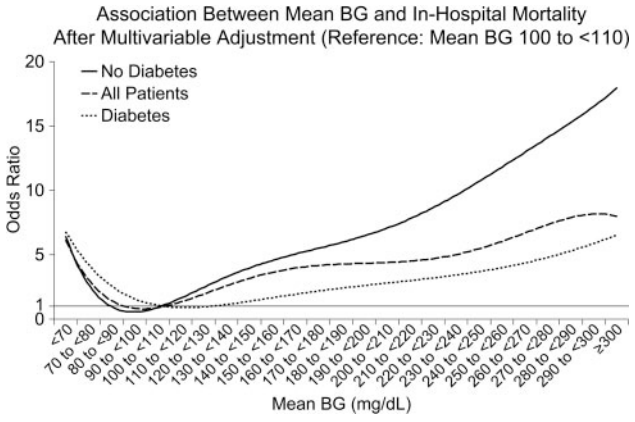

Figure 4. Nature of the relationship between mean hospitalization glucose and the odds of in-hospital mortality (adjusted analysis). BG indicates blood glucose.

Our results have significant implications for the field of "metabolic control" in patients hospitalized with AMI. Our data clearly imply that glucose values at any point during hospitalization are important and suggest that persistent hyperglycemia even after the initial acute phase of AMI should not be ignored. Specifically, we established that mean glucose is the most practical summary metric of glucose control during AMI. Given the ease of calculation and implementation, this simple metric could be used routinely in the monitoring and clinical management of patients with AMI. Such a "running average" of glucose values in individual patients, nursing units, and entire hospitals could be used for prognosis and performance assessment and, if an intervention is demonstrated to be prognostically beneficial, as a modifiable target for quality improvement.

Elevated admission and mean glucose levels may eventually be used to trigger a decision to institute intensive glucose control in hyperglycemic patients with AMI. Admittedly, because of the limitations of prior clinical trials,[34–38] the data concerning the benefits of glucose control in the setting of AMI are currently inconclusive, and randomized trials are needed to definitively establish whether intensive glucose control will improve survival in this patient population. From our results, however, we propose that mean glucose should be the metric that is used to evaluate the effectiveness of intensive glucose control in such clinical trials.

The differential impact of persistent hyperglycemia on mortality rates in patients with and without known diabetes was previously observed (with the metric of admission glucose).[1,14,20,39] Several potential explanations for this phenomenon exist. Some hyperglycemic patients without previously known diabetes likely have diabetes that was not appropriately recognized or treated before hospitalization; therefore, these patients may represent a higher-risk cohort. Second, as was previously suggested,[1] AMI patients without

known diabetes are much less likely to be treated with insulin in a setting of admission hyperglycemia than those with established diabetes, even when glucose levels are markedly elevated. It also is possible that higher degrees of stress (or severity of illness) are required to produce similar degrees of hyperglycemia in patients without known diabetes compared with those with established diabetes; however, the differential effect of persistent hyperglycemia continued in our study even after adjustment for measures of infarct size (such as peak troponin) and other comorbidities.

Finally, another important observation in our study was the markedly worse survival observed in patients with persistent in-hospital hypoglycemia compared with patients who had normal mean glucose. Although it is possible that this observed higher risk of death was due in part to other concomitant conditions associated with persistent hypoglycemia (eg, cardiogenic shock, sepsis, and liver failure), other investigators have previously found that even isolated hypoglycemic events are associated with adverse long-term outcomes.[22,40] Experience from randomized clinical trials in critically ill patients has shown that the rates of hypoglycemia associated with intensive glucose control are not negligible.[41,42] Until more detailed data are available from clinical trials of glucose control in AMI, interventions used to control glucose in this patient population must balance the potential benefits of glucose control against the potential risks of hypoglycemia.

The exact mechanisms behind the association of persistent hyperglycemia and higher in-hospital mortality have not been definitively established. However, prior physiological studies show that higher glucose levels in patients with AMI are associated with higher free fatty acid concentrations (which may induce cardiac arrhythmias), insulin resistance, and impaired myocardial glucose use, thus increasing the consumption of oxygen and potentially worsening ischemia.[43,44] Hyperglycemia also has been associated with microvascular dysfunction,[45,46] prothrombotic state,[47–53] vascular inflammation,[54–56] endothelial dysfunction,[57] and generation of reactive oxygen species.[58,59] All of these mechanisms may potentiate tissue injury in a setting of AMI.

The results of our study should be interpreted in the context of several possible limitations. First, given the retrospective nature of the analysis, residual unmeasured confounding cannot be entirely excluded, and whether persistent hyperglycemia is a marker or mediator of adverse events cannot be definitively determined in this observational study. Specifically, we were not able to control for several clinical variables such as left ventricular ejection fraction after AMI and the presence of ST-segment elevations. However, this limitation would not have affected the comparison of various glucose metrics because each of these metrics would be similarly confounded by these variables. Furthermore, adjustment for left ventricular ejection fraction did not have much impact on the prognostic effect of glucose in our prior analyses of admission glucose.[1] Importantly, we were able to control for other, more important measures of infarct severity such as peak troponin/creatine kinase-MB and multiple other clinical factors. Second, we were not able to determine how many patients without previously known diabetes on admission were diagnosed with diabetes during hospitalization or after discharge. Finally, because of limited follow-up, we could not assess the effect of persistent hyperglycemia on long-term outcomes.

Conclusions

Persistent hyperglycemia is a better discriminator of mortality than admission glucose alone in patients hospitalized with AMI. There is no critical time window regarding the detrimental effect of elevated glucose on mortality rates. Glucose control during the course of the entire hospitalization is incrementally important, and mean hospitalization glucose appears to be the most practical metric of average glucose control in this patient group. Both patients with persistent hyperglycemia and those with hypoglycemia are at increased risk of in-hospital death. Whether intensive glucose control in patients with AMI will result in improved survival remains to be tested in prospective randomized trials.

Disclosures

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CLINICAL PERSPECTIVE

Hyperglycemia on admission is a known risk factor for death in patients with acute myocardial infarction. Whether persistent hyperglycemia during acute myocardial infarction hospitalization is more prognostically important than admission hyperglycemia has not been well defined. Furthermore, the best summary measure of persistent hyperglycemia has not been developed. We evaluated 16 871 acute myocardial infarction patients who were hospitalized in 40 US medical centers from January 2000 to December 2005 and had comprehensive laboratory data. The performance of 3 alternative glucose control metrics (mean glucose, time-averaged glucose, and hyperglycemic index) was evaluated over 3 time windows (the first 24 hours, the first 48 hours, and the entire hospitalization) and compared with admission glucose for their ability to predict in-hospital death. We found that all measures of persistent hyperglycemia were better predictors of mortality than admission glucose. There was no "critical time window" that was most associated with death; glucose assessments over the entire hospitalization were incrementally better than assessments over shorter durations of time. Mean glucose was the most practical summary metric of glucose control during acute myocardial infarction given its ease of calculation. This simple metric could be used routinely for prognosis and, if an intervention is demonstrated to be prognostically beneficial, as a modifiable therapeutic target.