Original Article

Association Between Hyperglycemia and Increased Hospital Mortality in a Heterogeneous Population of Critically Ill Patients

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- *Objective*: To investigate the relationship between hyperglycemia and hospital mortality in a heterogeneous group of critically ill patients.
- *Patients and Methods*: Retrospective data were reviewed for 1826 consecutive patients whose glucose values were obtained during their intensive care unit stay at The Stamford Hospital in Stamford, Conn, between October 1, 1999, and April 4, 2002.
- *Results*: Mean and maximum glucose values were significantly higher among nonsurvivors than among survivors for the entire group ($P<.001$) and for each subgroup except for patients with septic shock. The lowest hospital mortality, 9.6%, occurred among patients with mean glucose values between 80 and 99 mg/dL. Hospital mortality increased progressively as glucose values increased, reaching 42.5% among patients with mean glucose values exceeding 300 mg/dL. Within each of 3 groupings of Acute Physiology and Chronic Health Evaluation II (APACHE II) scores (0-14; 15-24; ≥25), mean and maximum glucose values were higher among nonsurvivors than among survivors.
- *Conclusion*: Even a modest degree of hyperglycemia occurring after intensive care unit admission was associated with a substantial increase in hospital mortality in patients with a wide range of medical and surgical diagnoses. Analysis of glucose values added predictive power above that achieved by APACHE II scores alone. These results have important implications for the glycemic management of critically ill patients.

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APACHE = Acute Physiology and Chronic Health Evaluation; *ICD-9 = International Classification of Diseases, Ninth Revision*; ICU = intensive care unit; LOS = length of stay

Hyperglycemia occurs frequently in critically ill patients. Mechanisms include insulin resistance, absolute or relative insulin deficiency, impaired glucose metabolism, and the effect of medications such as corticosteroids and densely caloric enteral and parenteral nutritional supplements.[1]

Although hyperglycemia can be a marker of severity of illness, it also can worsen outcomes. Takala et al[2] reported that growth hormone therapy, which led to hyperglycemia and insulin resistance, was associated with a doubling of the mortality rate of a group of critically ill patients. Hyperglycemia also is associated with poor outcome in both diabetic and nondiabetic patients after stroke.[3-6] The plasma glucose value on admission has been shown to affect prognosis in a group of nondiabetic patients with acute myocardial infarction.[7]

Diabetic patients with myocardial infarction who underwent intensive glycemic management with insulin infusions followed by tightly controlled subcutaneous insulin administration had improved 1-year survival rates compared with a cohort who received standard glycemic management.[8] Similarly, continuous intravenous insulin infusion reduced the rate of sternal wound infections in a group of diabetic patients who underwent cardiac surgery.[2] Finally, Van den Berghe et al[9] recently described a 34% reduction in hospital mortality in a group of 1548 patients in a single surgical critical care unit with use of intensive insulin therapy to achieve euglycemia.

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The relationship between hyperglycemia and outcome in a heterogeneous group of critically ill patients has not been well described. This retrospective review of a large database from a single university-affiliated community hospital was undertaken to examine the effect of hyperglycemia on mortality in a heterogeneous population of critically ill adult patients admitted to an intensive care unit (ICU).

PATIENTS AND METHODS

Between October 1, 1999, and April 4, 2002, 2098 patients were admitted to The Stamford Hospital ICU. If a patient required readmission, only laboratory data and outcomes from the first admission were included. Plasma glucose

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Table 1. **Description of Patient Subgroups (N=1826)***

Subgroup	No. of patients	% of total†
Cardiac	540	29.6
Myocardial infarction	198	
Congestive heart failure	136	
Cardiac arrest	57	
Intermediate coronary syndrome	51	
Rhythm disturbance	50	
Hypertension	27	
Cardiogenic shock	13	
Miscellaneous	8	
Pulmonary	289	15.8
Pneumonia	92	
COPD	51	
Aspiration pneumonitis	28	
Pulmonary embolism	14	
Asthma	11	
Multifactorial respiratory failure with cancer	23	
Miscellaneous	70	
Septic shock‡	92	5.0
Nonurinary source	75	
Urosepsis	17	
Other medical	272	14.9
Gastrointestinal	128	
Metabolic	75	
Renal	25	
Miscellaneous	44	
Neurologic§	241	13.2
Intracerebral hemorrhage	48	
CVA or TIA	35	
Craniotomy for neoplasm	34	
Subdural or epidural hematoma	31	
Seizure	29	
Spinal surgery	28	
Subarachnoid hemorrhage	17	
Miscellaneous	19	
General surgical	313	17.1
Gastrointestinal	122	
Vascular	83	
Thoracic	52	
Miscellaneous	56	
Trauma	79	4.3
Nonoperative	44	
Operative	35	

*COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular accident; TIA = transient ischemic attack.
†Percentages do not equal 100% because of rounding.
‡Defined by criteria established by the consensus conference of the American College of Chest Physicians and the Society of Critical Care Medicine.[10]
§Includes operative and nonoperative patients.

values were not obtained in 144 patients during their ICU stay, and complete records of final *International Classification of Diseases, Ninth Revision* (*ICD-9*) codes were not available for 128 patients. The remaining 1826 patients constitute the subject of this report.

The Stamford Hospital is a not-for-profit community hospital that serves as a major teaching affiliate of Columbia University College of Physicians and Surgeons. The Stamford Hospital ICU treats a heterogeneous population of general medical, surgical, and coronary patients. The director of critical care and the director of surgery oversee medical and surgical house staff in the care of patients and in writing all patient orders. The ICU has an "open" configuration: primary care physicians may admit patients to the unit, but appropriate organ-specific subspecialty or critical care consultations are obtained for all patients.

The diagnostic groups within each patient subgroup are shown in Table 1.[10]

Databases

We use a comprehensive database to track multiple outcomes for all patients admitted to the ICU. The core dataset is maintained and updated daily by the director of critical care and an associate, who ensure data integrity and completeness. Data included in this report include length of stay (LOS) in 0.1-day increments, Acute Physiology and Chronic Health Evaluation II (APACHE II) score based on the first 24 hours after ICU admission,[11] age, and primary ICU diagnosis. The director of critical care assigns a primary diagnosis at the time of ICU admission on the basis of the 80+ APACHE III diagnostic categories,[12] which are more detailed and numerous than those found in the APACHE II system. A modified APACHE II score is calculated by deleting the age component from the APACHE II score to analyze separately the contributions of acuity of illness and age to mortality. This database is linked to multiple hospital databases with queries, allowing linkage of the central core of information with discharge status, *ICD-9* codes assigned at the time of discharge, and laboratory data obtained during the ICU stay.

Measurements

During patients' ICU stay, all plasma glucose values were obtained with use of a query linking the master database to the laboratory database, and the final discharge status for each patient was ascertained. A single value representing the mean of these glucose values was assigned to each patient and correlated with final discharge status. The initial and maximum glucose values obtained during ICU stay also were abstracted from the database for separate analysis. The terms *survivor* and *nonsurvivor* relate to hospital discharge status, not ICU discharge status. All plasma glucose assays were performed using Vitros 950 and Vitros 250 chemistry analyzers (Ortho-Clinical Diagnostics, Raritan, NJ, a division of Johnson & Johnson).

Statistical Analyses

Statistical analysis was performed using the SPSS 11.0 statistical package. Glucose values, age, LOS, and APACHE II scores were expressed as mean and range and

Table 2. **Description of Patients***

Patient subgroup	No. of patients	Age (y)	Female (%)	APACHE II score	Mech vent (%)	LOS (d)	Hospital survival (%)
All patients	1826	65.3 (13-100)	45.6	16.9 (0-51)	36.6	3.87 (0.0-79.0)	81.0
Cardiac	540	68.6 (22-100)	42.6	15.5 (0-50)	27.2	2.79 (0.1-79.0)	86.7
Pulmonary	289	70.1 (15-98)	47.1	21.4 (6-46)	61.6	6.07 (0.3-35.8)	65.7
Septic shock	92	66.5 (19-95)	56.5	28.0 (12-51)	55.4	5.82 (0.3-52.1)	55.4
Other medical	272	60.9 (14-98)	43.4	17.7 (0-44)	28.3	3.72 (0.1-60.0)	83.8
Neurologic	241	61.3 (17-100)	56.4	14.3 (1-48)	28.6	3.36 (0.3-30.9)	83.8
General surgical	313	67.2 (16-96)	44.7	14.2 (0-46)	37.1	3.75 (0.0-39.0)	86.6
Trauma	79	44.1 (13-88)	26.6	11.9 (0-37)	39.2	3.36 (0.1-17.0)	87.3

*Age, APACHE II scores, and LOS expressed as mean (range). APACHE = Acute Physiology and Chronic Health Evaluation; LOS = length of stay; Mech vent = mechanical ventilation.

were compared between survivors and nonsurvivors with use of the Wilcoxon test for populations without normal distribution. Because LOS was measured in 0.1-day increments, the shortest LOS abstracted from the database was 0.0 days (total LOS in the ICU <1 hour). Comparisons of the percentage of patients in different subgroups requiring mechanical ventilation were performed using the χ^2 statistic, which also was used to test for the trend of increasing hospital mortality with increasing mean glucose levels and to assess differences in mortality rates among groups of patients. Multiple stepwise logistic regression analysis was used to assess the effect on hospital mortality of APACHE II scores, APACHE II scores with the age component deleted ("modified APACHE II score"), age, glucose values, need for mechanical ventilation, and LOS. Statistical significance was defined as $P<.05$; all results were 2-tailed.

The Stamford Hospital Institutional Review Board approved this study.

RESULTS

Baseline Characteristics and Selected Outcomes

Selected characteristics of the 1826 patients and the different subgroups are described in Table 2. APACHE II scores reflect data obtained during the first 24 hours after admission. A total of 27 patients (1.48%) were between age 13 and 19 years. Patients with septic shock had the highest APACHE II scores and the lowest hospital survival. Patients with pulmonary diseases had the longest ICU LOS and the highest percentage of mechanical ventilation. Sex had no effect on severity-adjusted survival (Table 3).

Comparisons of Survivors and Nonsurvivors

Survivors were compared with nonsurvivors for each subgroup and for the entire group (Table 4). Survivors had lower APACHE II scores than did nonsurvivors in all patient subgroups ($P<.001$ for all comparisons). Nonsurvivors were older than survivors in all patient subgroups except for the septic shock and trauma subgroups. The percentage of patients requiring mechanical ventilation was significantly greater among nonsurvivors than among survivors in every patient subgroup ($P<.001$). The mean ICU LOS was significantly greater ($P<.001$) for nonsurvivors than for survivors in all subgroups except for those in septic shock, neurologic, and trauma subgroups, among whom there was no significant difference.

Glucose Values and Hospital Mortality

The mean of all glucose values obtained during each patient's ICU stay was calculated, and this single value was assigned to each patient, regardless of the number of separate assays obtained. The number of glucose values obtained for each patient correlated significantly with the patient's LOS ($R = 0.870$; $P<.001$).

Mean, initial, and maximum glucose values obtained for survivors and nonsurvivors during the ICU stay are compared in Table 5. Mean and maximum glucose values were significantly higher for nonsurvivors than for survivors for the entire population and for each subgroup except for patients with septic shock. Striking differences in mean glucose values between survivors and nonsurvivors were revealed when results were stratified by age (Table 6). Initial glucose values were significantly higher among nonsurvivors than among survivors for the entire population and for most of the subgroups (Table 5).

Table 3. **Sex and Severity-Adjusted Survival (N=1826)***

APACHE II score	Male		Female		*P* value
	No. of patients	Survival (%)	No. of patients	Survival (%)	
0-14	484	95.0	359	96.4	.44
15-24	321	80.4	320	80.0	.98
25+	183	43.2	159	50.3	.22
Total	988	80.7	838	81.4	.74

*APACHE = Acute Physiology and Chronic Health Evaluation.

Table 4. **Comparison of Selected Baseline Features and Outcomes in Survivors and Nonsurvivors (N=1826)***

Patient subgroup	No. of patients	Age (y)	APACHE II score	Mech vent (%)	LOS (d)
All					
Survivors	1479	64.2 (13-100)	14.7 (0-44)	28.7	3.35 (0.1-60.0)
Nonsurvivors	347	70.1 (18-98)	26.1 (6-51)	70.6	6.04 (0.0-79.0)
Cardiac					
Survivors	468	67.8 (22-100)	13.5 (0-42)	19.7	2.36 (0.2-21.3)
Nonsurvivors	72	73.9 (33-93)	28.3 (9-50)	76.3	5.60 (0.1-79.0)
Pulmonary					
Survivors	190	68.4 (15-98)	19.6 (6-38)	54.2	5.07 (0.3-34.9)
Nonsurvivors	99	73.5 (18-94)	24.9 (13-46)	75.8	7.98 (0.3-35.8)
Septic shock					
Survivors	51	67.6 (34-95)	24.2 (12-44)	41.1	5.14 (0.6-20.0)
Nonsurvivors	41	65.1 (19-89)	32.8 (19-51)	73.2	6.66 (0.3-52.1)
Other medical					
Survivors	228	59.9 (14-97)	16.1 (0-40)	23.2	3.46 (0.4-60.0)
Nonsurvivors	44	66.1 (33-98)	25.9 (10-44)	54.5	5.11 (0.1-22.8)
Neurologic					
Survivors	202	59.9 (17-100)	12.6 (1-35)	23.3	3.47 (0.5-30.9)
Nonsurvivors	39	68.9 (30-94)	22.8 (6-48)	56.4	2.75 (0.3-7.1)
General surgical					
Survivors	271	66.5 (16-96)	13.0 (0-43)	31.7	3.29 (0.1-39.0)
Nonsurvivors	42	71.9 (24-91)	21.7 (8-46)	71.4	6.76 (0.0-28.8)
Trauma					
Survivors	69	44.0 (13-88)	9.6 (0-28)	31.9	3.62 (0.5-17.0)
Nonsurvivors	10	45.0 (19-73)	27.7 (12-37)	90.0	1.60 (0.1-3.5)

*Age, APACHE II scores, and LOS expressed as mean (range). APACHE = Acute Physiology and Chronic Health Evaluation; LOS = length of stay; Mech vent = mechanical ventilation.

Of the 1826 patients whose records were reviewed, 24 (1.31%) had an ICU LOS less than 0.5 day. Among these patients, the 11 survivors had a mean glucose value of 156.9 mg/dL (range, 99.5-342.0 mg/dL), and the 13 nonsurvivors had a mean glucose value of 299.7 mg/dL (range, 74.0-1183.0 mg/dL) (P=.12).

The relationship of hospital mortality to mean serum glucose values obtained during the ICU stay for patients with mean serum glucose values of 80 mg/dL or greater is shown in Table 7. The lowest hospital mortality, 9.6%, occurred among patients with mean glucose values between 80 and 99 mg/dL. Patients with mean glucose values of 100 to 119 mg/dL, still within the normal range for this laboratory test, had a 27% increase in hospital mortality compared with those with mean glucose values of 80 to 99 mg/dL. Hospital mortality increased progressively with further increases in mean glucose values, with the highest hospital mortality (42.5%) noted among patients with mean glucose values exceeding 300 mg/dL (χ^2 for trend, P<.001). There was a similar relationship between mean plasma glucose and hospital survival for each patient subgroup (χ^2 for trend, P<.001) except for the patients in the pulmonary subgroup. The 35 patients (1.92%) with mean glucose values less than 80 mg/dL had a 22.9% hospital mortality rate.

Relationship of Diabetes to Glucose Values and Hospital Mortality

The presence of diabetes was ascertained using *ICD-9* codes assigned at hospital discharge. Diabetes was present in 22.4% of the entire population. The highest prevalence of diabetes was observed in the cardiac subgroup (29.2%), whereas the lowest was seen in the trauma subgroup (5.1%). For the entire group, there was no difference in mortality based on the presence or absence of diabetes. Hospital mortality was higher among diabetic patients in the neurologic subgroup (P<.001) but not statistically different for any of the other groups.

Mean glucose values were higher among diabetic nonsurvivors than among diabetic survivors (201.2 mg/dL [range, 27.0-404.8 mg/dL] vs 187.8 mg/dL [range, 54.0-642.3 mg/dL]; P=.03). The difference in mean glucose values between nondiabetic nonsurvivors and nondiabetic survivors was even greater (162.8 mg/dL [range, 53.7-1183.0 mg/dL] vs 123.8 mg/dL [range, 59.0-363.0 mg/dL]; P<.001). Furthermore, the difference between the mean glucose values of survivors and nonsurvivors was significant for each subgroup of nondiabetic patients. In contrast, the difference in mean glucose values between survivors and nonsurvivors among diabetic patients was much less

Table 5. **Comparison of Mean, Initial, and Maximum Glucose Values in Survivors and Nonsurvivors*†**

Patient subgroup	Mean (mg/dL)	*P* value	Initial (mg/dL)	*P* value	Maximum (mg/dL)	*P* value
All						
Survivors	137.9 (54.0-642.3)	<.001	150.5 (22-1218)	.001	177.1 (54-1371)	<.001
Nonsurvivors	172.0 (27.0-1183.0)		174.7 (25-1183)		257.9 (27-1183)	
Cardiac						
Survivors	136.2 (54.0-495.0)	<.001	146.3 (52-695)	.001	165.3 (54-1371)	<.001
Nonsurvivors	196.8 (76.7-1183.0)		215.8 (29-1183)		268.1 (90-1183)	
Pulmonary						
Survivors	145.1 (60.1-351.5)	.04	148.2 (45-436)	.11	196.2 (60-948)	<.001
Nonsurvivors	155.1 (27.0-286.0)		164.4 (27-496)		242.6 (27-640)	
Septic shock						
Survivors	147.2 (72.5-335.0)	.25	162.8 (56-428)	.01	209.8 (89-590)	.17
Nonsurvivors	161.4 (65.0-443.8)		128.3 (25-388)		260.7 (65-1024)	
Other medical						
Survivors	138.2 (59.0-404.0)	.04	168.3 (33-1168)	.24	195.7 (59-1168)	.007
Nonsurvivors	163.3 (64.0-403.0)		144.1 (27-591)		247.6 (74-788)	
Neurologic						
Survivors	139.6 (73.8-642.3)	<.001	149.6 (32-1218)	<.001	173.4 (79-1218)	<.001
Nonsurvivors	187.1 (53.7-359.6)		195.0 (47-552)		255.2 (72-1017)	
General surgical						
Survivors	134.9 (66.0-342.0)	<.001	144.7 (22-769)	.007	170.5 (68-1155)	<.001
Nonsurvivors	169.1 (85.3-404.8)		177.0 (69-421)		277.4 (93-779)	
Trauma						
Survivors	129.6 (79.0-264.6)	.007	142.2 (79-448)	.04	154.5 (79-470)	.001
Nonsurvivors	197.5 (110.6-349.0)		214.4 (65-487)		299.2 (145-700)	

*Glucose values expressed as mean (range).
†Survivors and nonsurvivors for each group were compared using the Wilcoxon test for unpaired values that are not normally distributed.

striking: although statistically significant for the entire group of diabetic patients, it did not reach statistical significance in any single patient subgroup. The difference in mean glucose values between all survivors and all nonsurvivors is largely attributable to the findings from nondiabetic patients.

Relationship of Glucose Values and APACHE II Scores

Glucose values increased with increasing APACHE II scores. Among the entire patient group, the mean glucose value was 130.4 mg/dL (range, 59.0-404.8 mg/dL) for patients with APACHE II scores 0-14; 149.2 mg/dL (range, 27.0-642.3 mg/dL) for patients with APACHE II scores 15-24; and 169.8 mg/dL (range, 53.7-1183.0 mg/dL) for patients with APACHE II scores of 25 or greater ($P<.001$ for all comparisons). Within each grouping of APACHE II scores, nonsurvivors had higher mean and maximum glucose values than did survivors (Table 8), and hospital mortality increased with increasing mean glucose values greater than 80 to 119 mg/dL (χ^2 for trend APACHE II score 0-14, $P=.001$; APACHE II score 15-24, $P=.001$; APACHE II score ≥25, $P=.01$). Initial glucose values were higher among nonsurvivors than among survivors only among patients with APACHE II scores 0-14; initial glucose values of patients with higher APACHE II scores were not significantly different.

Multiple Stepwise Logistic Regression Analysis of Factors Relating to Hospital Mortality and ICU LOS

Results of multiple stepwise logistic regression analyses are presented in Table 9. A modified APACHE II score, eliminating the age component from the APACHE II calculation, was used to analyze separately the contributions of age and acuity of illness to mortality. Modified APACHE II score, age, mean glucose value, and the need for mechanical ventilation were associated with hospital mortality ($R = 0.517$, $P<.001$); the modified APACHE II score contributed the greatest amount to the model. Sex and ICU LOS were not significantly associated with mortality.

Univariate regression revealed that mechanical ventilation ($P<.001$) and modified APACHE II score ($P=.01$) were significantly associated with ICU LOS. Mean glucose value, age, and sex were not significantly associated with ICU LOS.

DISCUSSION

The salient finding of this investigation is that even a modest elevation of mean glucose levels occurring during ICU stay was associated with increased hospital mortality

Table 6. **Relationship of Age to Survival and Mean Glucose Level (N=1826)***

Age (y)	No. of patients	Mean glucose value (mg/dL)		*P* value
		Survivors	Nonsurvivors	
13-49	367	128.4 (59.0-334.2)	197.3 (53.7-1183.0)	<.001
50-64	358	140.3 (73.8-495.0)	190.8 (67.7-448.0)	<.001
65-79	670	145.6 (60.0-642.3)	170.3 (64.0-404.8)	<.001
80+	431	133.0 (54.0-404.0)	153.7 (27.0-513.3)	<.001

*Values are expressed as mean (range).

in a heterogeneous population of critically ill patients. The retrospective design prevents conclusions regarding whether hyperglycemia was a cause of increased mortality or rather just a marker of increased risk of mortality. Nevertheless, the strong association between hospital mortality and glycemic levels, which has potentially important clinical implications, extended from the entire population through the subgroups. The lowest hospital mortality, 9.6%, occurred among patients with mean glucose values between 80 and 99 mg/dL. Among patients with mean glucose values between 100 and 119 mg/dL, still within the normal range for this laboratory test, mortality increased to 12.2%, representing a 27% relative increase. Further increases in mean glucose had a progressively deleterious association with hospital mortality, culminating in 42.5% hospital mortality among patients with mean glucose values exceeding 300 mg/dL ($P<.001$ for trend). An analysis of maximum glucose values instead of mean glucose values during ICU stay yielded similar results, but initial glucose levels were somewhat less predictive. Furthermore, analysis of glucose values added predictive power for hospital mortality beyond that achieved by APACHE II scoring alone, a finding not reported previously. Within APACHE II groupings of 0 to 14, 15 to 24, and 25 or greater, glucose values were higher among nonsurvivors than among survivors. Finally, multiple stepwise logistic regression analysis confirmed that increasing APACHE II scores and increasing mean glucose values were independent predictors of hospital mortality.

Table 7. **Hospital Mortality Rate and Mean Glucose Value**

Mean* (mg/dL)	Mortality rate (%)	No. of patients
80-99	9.6	264
100-119	12.2	491
120-139	15.1	338
140-159	18.8	202
160-179	28.4	141
180-199	29.4	102
200-249	37.5	144
250-299	32.9	70
>300	42.5	40

*Glucose values expressed as a range of mean values. The χ^2 test was used for trend ($P<.001$).

The main strength of the study is the large number of patients who were evaluated, which provided the opportunity for extensive subgroup analysis. Other strengths include the detailed and accurate diagnostic breakdown and the extensive descriptive data and outcome data available from the linked databases. Moreover, the heterogeneous nature of the population makes the data applicable to other mixed medical-surgical ICU settings. Finally, the data are robust: the difference in mean glucose values between survivors and nonsurvivors was substantial—137.9 mg/dL (range, 54.0-642.3 mg/dL) vs 172.0 mg/dL (range, 27.0-1183.0 mg/dL) ($P<.001$)—and the large size of the subgroups allowed analysis with confidence.

The main limitation of this study is its retrospective nature. This design prevented uniformity in the collection of serum glucose values for individual patients. The number of glucose values obtained correlated strongly with the patient's LOS in the ICU ($R = 0.870$; $P<.001$), and a single value representing the mean of the individual assays was assigned to each patient. Inferences were based on this single mean value, although there were variable numbers of individual tests and indications for obtaining them. A separate analysis of hospital mortality related to maximum glucose value obtained during the ICU stay revealed the same strong relationship; the mean glucose value was chosen as the primary variable instead of the maximum glucose value because the mean value more closely approximated overall glycemic control during ICU stay.

Another limitation was that the diagnosis of diabetes was derived from the *ICD-9* codes assigned at hospital discharge by hospital coders. Although it is unlikely that diabetes was diagnosed incorrectly in any patient, some patients who developed hyperglycemia during their ICU stay possibly had latent diabetes that was not correctly designated as such.

Finally, the study period was 30 months, and consecutive admissions were analyzed. Data relating to *ICD-9* diagnoses were not available for 128 of the 2098 patients admitted; for an additional 144 patients, no serum glucose values were obtained during their ICU stay. However, if the data from the 128 patients (6.1%) with missing *ICD-9* diagnoses had been included, it probably would not have altered the main findings of the study.

Other investigators have noted that hyperglycemia is a marker of poor outcome in specific clinical contexts. A substantial body of evidence supports this association among patients with neurologic disease. Young et al[5] described the relationship between hyperglycemia at admis-

Table 8. **Mean, Initial, and Maximum Glucose Values and APACHE II Scores (N=1826)***

APACHE II score	No. of patients	Mean (mg/dL)	*P* value†	Initial (mg/dL)	*P* value†	Maximum (mg/dL)	*P* value†
Survivors							
0-14	806	128.8 (59.0-402.0)	<.001	136.5 (56-603)	.002	148.7 (59-603)	<.001
15-24	514	146.2 (54.0-642.3)	.001	162.4 (33-1218)	.91	197.6 (54-1218)	<.001
25+	159	157.4 (67.3-495.0)	.02	183.2 (22-1168)	.78	254.4 (76-1371)	.06
Nonsurvivors							
0-14	37	165.3 (82.3-404.8)	<.001	173.4 (73-421)	.002	231.8 (94-668)	<.001
15-24	127	161.5 (27.0-380.5)	.001	153.6 (27-386)	.91	239.6 (27-1017)	<.001
25+	183	180.7 (53.7-1183.0)	.02	153.6 (27-386)	.78	275.9 (65-1183)	.06

*Glucose values expressed as mean (range). APACHE = Acute Physiology and Chronic Health Evaluation.
†*P* values compare survivors vs nonsurvivors, using the Wilcoxon test for unpaired values that are not normally distributed.

sion and neurologic outcome among 59 patients with traumatic brain injury. Patients with peak glucose values greater than 200 mg/dL within 24 hours of admission had worse Glasgow Coma Scale scores at 18 days, 3 months, and 1 year than did patients with peak glucose values less than 200 mg/dL.

Weir et al[3] studied a consecutive series of 645 patients with ischemic stroke and 105 patients with hemorrhagic stroke. The presence of hyperglycemia predicted increased mortality and morbidity, even when corrected for age, stroke severity, and stroke subtype.

Finally, Demchuk et al[13] found that hyperglycemia predicted the development of intracerebral hemorrhage after thrombolytic therapy for ischemic stroke. Hyperglycemia also has been implicated as a predictor of worsened outcome in cardiac surgery patients. Fietsam et al[14] reported increased wound infection, arrhythmia, and respiratory failure among 146 diabetic patients compared with 565 nondiabetic patients who underwent coronary artery bypass grafting surgery. Mean glucose values among the diabetic patients who had postoperative complications in this series exceed those of the diabetic patients without complications. Glucose values for the nondiabetic patients were not reported.

Several investigators have evaluated the role of intensive glycemic management in different patient populations. Perioperative glucose values and sternal wound infection rates were significantly lower among 1499 diabetic patients who underwent cardiac surgery and were treated with continuous insulin infusions compared with 968 diabetic patients who underwent similar surgery and received standard subcutaneous insulin on the basis of a sliding-scale protocol.[15] Similarly, 620 diabetic patients with acute myocardial infarction were randomized to insulin infusion followed by intensive subcutaneous insulin administration vs standard care (the Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction [DIGAMI] study).[8] Plasma glucose values obtained during hospitalization were significantly lower in the treatment group than in the control group, and the 1-year mortality rates were 18.6% and 26.1%, respectively (29% relative mortality reduction; *P*=.03). More recently, Van den Berghe et al[9] reported their investigation of intensive glucose control in a group of patients requiring mechanical ventilation in the surgical ICU for more than 5 days. They used insulin infusions if needed in the treatment arm to achieve glucose levels between 80 and 110 mg/dL. The ICU mortality rate decreased from 8.0% to 4.6%, and the patients treated in the ICU had a significant decrease in the requirement for hemodialysis and blood transfusions and a reduction in the incidence of critical-illness polyneuropathy.

CONCLUSION

This investigation showed that even a modest degree of hyperglycemia occurring during ICU stay was associated with increased hospital mortality in a heterogeneous group of critically ill patients. Hospital mortality was lowest among patients with mean serum glucose values between 80 and 99 mg/dL and increased significantly and progressively as mean serum glucose values exceeded this range. Analysis of maximum glucose values obtained during each patient's ICU stay revealed the same association. The differences in mean glucose values between survivors and nonsurvivors were greater among nondiabetic patients than among diabetic patients. These differences occurred at significantly lower mean glucose values among the nondiabetic patients than among the diabetic patients.

Table 9. **Multiple Stepwise Logistic Regression Analysis of Factors Associated With Hospital Mortality***

Factor	Standardized regression correlation	*P* value
Modified APACHE II	–.396	<.001
Mechanical ventilation	–.130	<.001
Age	–.100	<.001
Mean glucose	–.081	<.001

*APACHE = Acute Physiology and Chronic Health Evaluation.

Multiple stepwise logistic regression analysis confirmed that hyperglycemia was an independent risk factor for increased hospital mortality. Even among patients with similar APACHE II scores, the mean glucose values were higher in nonsurvivors than among survivors, suggesting that the measurement of serum glucose values provided additional discriminative power to this standard mortality prediction model. Although this investigation was not designed to assess whether hyperglycemia was a cause of increased hospital mortality or just an epiphenomenon, these findings provide a compelling justification for conducting trials of intensive glycemic management in a heterogeneous population of critically ill patients.

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