Impact of admission hyperglycemia on hospital mortality in various intensive care unit populations*

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Objective: **Hyperglycemia in intensive care unit patients has been associated with an increased mortality rate, and institutions have already begun tight glucose control programs based on a limited number of clinical trials in restricted populations. This study aimed to assess the generalizability of the association between hyperglycemia and in-hospital mortality in different intensive care unit types adjusting for illness severity and diabetic history.**

Design: **Retrospective cohort study.**

Setting: **The medical, cardiothoracic surgery, cardiac, general surgical, and neurosurgical intensive care units of the University of Maryland Medical Center.**

Patients: **Patients admitted between July 1996 and January 1998 with length of stay ≥24 hrs (n = 2713).**

Interventions: **On intensive care unit admission, blood glucose and other physiologic variables were evaluated. Regular measurements were taken for calculation of Acute Physiology and Chronic Health Evaluation III scoring. Patients were followed through hospital discharge. Admission blood glucose was used to classify patients as hyperglycemic (>200 mg/dL) or normoglycemic (60–200 mg/dL). The contribution of hyperglycemia to in-hospital mortality stratified by intensive care unit type and diabetes history while controlling for illness severity was estimated by logistic regression.**

Measurements and Main Results: **The adjusted odds ratios for death comparing all patients with hyperglycemia to those without were 0.81 (95% confidence interval, 0.37, 1.77) and 1.76 (95% confidence interval, 1.23, 2.53) for those with and without diabetic history, respectively. Higher mortality was seen in hyperglycemic patients without diabetic history in the cardiothoracic, (adjusted odds ratio, 2.84 [1.21, 6.63]), cardiac (adjusted odds ratio, 2.64 [1.14, 6.10]), and neurosurgical units (adjusted odds ratio, 2.96 [1.51, 5.77]) but not the medical or surgical intensive care units or in patients with diabetic history.**

Conclusions: **The association between hyperglycemia on intensive care unit admission and in-hospital mortality was not uniform in the study population; hyperglycemia was an independent risk factor only in patients without diabetic history in the cardiac, cardiothoracic, and neurosurgical intensive care units. (Crit Care Med 2005; 33:2772–2777)**

KEY WORDS: hyperglycemia; diabetes mellitus; intensive care unit; mortality; effect modification

Chronic hyperglycemia in patients with diabetes is known to be associated with increased morbidity and mortality rates (1). The impact of hyperglycemia on mortality rate in critically ill hospitalized patients has been increasingly appreciated. The association between hyperglycemia and increased risk of in-hospital mortality in such patients has been demonstrated in observational studies (2–5). Additional evidence suggests that the association between hyperglycemia and mortality may be stronger in critically ill patients without a previously recognized diagnosis of diabetes (2, 6–8). A recent randomized, controlled trial completed in a surgical intensive care unit (ICU) in Belgium showed a 42% reduction in the relative risk of ICU mortality in the group randomized to tight glucose control by insulin infusion therapy during the ICU stay; this study population comprised mostly nondiabetics, with 13% having a history of diabetes (9).

Despite the available evidence, it is not clear whether the relation between acute hyperglycemia and increased mortality risk is consistent for all critically ill hospitalized patients. Most of the observational studies have included data from cardiovascular disease patients (cardiac, cardiothoracic, and stroke) (2–4, 6, 10), whereas the trial by Van den Berghe and colleagues (9) was conducted in a surgical ICU that included a large number of cardiac and thoracic surgery patients. Beyond these patient groups, there is a paucity of data.

Furthermore, in evaluating hyperglycemia as a risk factor for mortality in critically ill patients, it is important to address the issue of illness severity. "Stress hyperglycemia" occurs in reaction to acute injury or illness, comprising a cascade of hormonal responses that result in gluconeogenesis, lipolysis, and hyperglycemia (11). However, the precise relation between hyperglycemia and

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Table 1. Characteristics of the study population, intensive care unit (ICU) patients at the University of Maryland Medical Center, 1996–1998, means and percent by admission hyperglycemia

	Hyperglycemia[a] n = 743 (27.4%)	Normoglycemia n = 1970 (72.6%)	Total n = 2713
Age, yrs, mean (SD)[b]	59.7 (14.6)	57.0 (16.2)	57.7 (15.8)
Gender, n (%)[c]			
Female	359 (29.9)	841 (70.1)	1200
Male	384 (25.4)	1129 (74.6)	1513
Race, n (%)			
White	470 (27.1)	1267 (72.9)	1737
Black	234 (28.4)	589 (71.6)	823
Asian/Hispanic	4 (40.0)	6 (60.0)	10
Unknown	35 (24.5)	108 (75.5)	143
ICU, n (%)[d]			
Surgical	224 (36.1)	397 (63.9)	621
Cardiac	122 (22.3)	424 (77.7)	546
Cardiothoracic	233 (31.2)	513 (68.8)	746
Neurosurgical	94 (20.8)	358 (79.2)	452
Medical	70 (20.1)	278 (79.9)	348
Diabetes, n (%)[c]			
Yes	348 (60.6)	226 (39.4)	574
No	395 (18.5)	1744 (81.5)	2139
Length of stay, mean (SD)[b]	12.2 (13.3)	10.5 (11.7)	11.0 (12.2)
APACHE III score, mean (SD)[b,e]	44.3 (24.2)	31.7 (20.8)	35.1 (21.0)

APACHE, Acute Physiology and Chronic Health Evaluation.

[a]Hyperglycemia is defined as glucose >200 mg/dL on the first day of ICU visit; [b]$p < .05$ for Student's t-test of equality of group means; [c]$p < .05$ for χ^2 test for 2×2 contingency tables; [d]$p < .05$ for χ^2 test of independence; [e]APACHE III was taken from ICU day 1 and modified to exclude glucose points.

severity of illness is not always clear. Chronic hyperglycemia is known to have adverse effects on health via multiple mechanisms (12–17). Evaluation of the effect of hyperglycemia on risk of in-hospital mortality suggests the need for adjustment for illness severity.

We aimed to assess the generalizability of the association between admission hyperglycemia and in-hospital mortality in critically ill patients. If an association exists in only a subset of critically ill patients, then targeted interventions could be developed to treat those subpopulations most inclined to benefit. To this end, we used a cohort of ICU patients to examine the association between admission hyperglycemia and in-hospital mortality, stratifying by history of diabetes and type of ICU as a proxy for class of medical condition and controlling for illness severity.

MATERIALS AND METHODS

Study Population. The University of Maryland Medical Center (UMMC) is a teaching hospital with 656 total beds; included in this total are ten beds in the medical ICU (MICU), 12 beds in the cardiothoracic surgery ICU (CTICU), 15 beds in the cardiac ICU (CICU), 19 beds in the surgical ICU (SICU), and ten beds in the neurosurgical ICU (NSICU). The study used a previously assembled cohort that included patients admitted to these ICUs at UMMC during an 18-month period (July 1996 to January 1998) with an ICU stay of ≥24 hrs. Patients with hypoglycemia at admission to the ICU (blood glucose <60 mg/dL) were excluded. The first admission was used for patients with multiple ICU admissions. Individuals lacking information at admission glucose, discharge status, history of diabetes, or Acute Physiology and Chronic Health Evaluation (APACHE) III score were also excluded. The protocol, including all data collection and analysis methods, was reviewed by the institutional review board at the UMMC and was deemed exempt due to the nature of data collection and use; for more information, see (18), category 4 of 45CFR part 46.101b.

Data were collected as part of a hospital-wide quality improvement project. Variables in the dataset included age, gender, race, admitting diagnosis, ICU type, admission blood glucose, history of diabetes, APACHE III score, and in-hospital mortality. Data were collected by nursing staff in the ICU and entered by hospital clerical staff. A fulltime nurse coordinator performed data entry quality assurance and validation.

Consistent with the American Diabetes Association (19) recommendations and previous studies (3, 4, 20), hyperglycemia was defined as casual (nonfasting) blood glucose of >200 mg/dL on the day of admission to the ICU. We considered normoglycemia as admission glucose >60 mg/dL but ≤200 mg/dL. The highest blood glucose from peripheral blood draws on day 1 of ICU admission was used as the admission value.

Severity of illness was measured by the APACHE III score on the day of admission to the ICU. The APACHE was developed for prediction of hospital mortality risk among critically ill patients (21). We removed the points contributed by blood glucose to the APACHE score for the current study to avoid its inclusion twice in statistical models; this modified APACHE III score was used in analyses to control for severity of illness.

Data Analysis. Descriptive statistics were computed to assess the study sample's characteristics. Differences between those with hyperglycemia and those with normoglycemia were assessed by chi-square or Student's t-test, as appropriate. Those who survived for the length of the study were similarly compared with those who did not. Potential confounding was assessed using the Cochran-Mantel-Haenzel common odds ratio; a 10% change from the unadjusted odds ratio was considered as confounding. We evaluated nonhomogeneity of the association between hyperglycemia and mortality within strata of ICU type and history of diabetes by the Breslow-Day test of homogeneity. Significant departure from homogeneity indicates presence of effect modification and suggests that the results should not be collapsed across strata but rather presented separately. Multiple logistic regression was used to estimate adjusted, stratum-specific odds ratios. Modifiers of the association (odds ratio) of hyperglycemia and death were included as interaction terms in these models. Residuals from regression of the recalculated APACHE III on hyperglycemia were included in the multivariable logistic regression to adjust for disease severity. Since several definitions of the threshold for hyperglycemia have been used, a sensitivity analysis was performed with a threshold of 150 mg/dL to evaluate the effect of the choice of blood glucose cut point used to define hyperglycemia. The level of statistical significance was set at .05. Data analysis was performed using SAS version 8.2.

RESULTS

During the 18-month period, 3,678 patients were admitted to one of the five ICUs. Subjects with missing information for admission glucose (n = 582), status at ICU discharge (n = 275), and/or admission APACHE III score (n = 60) were excluded from further analysis. Although of clinical interest, those with hypoglycemia (n = 48) were excluded due to their insufficient numbers for the planned analysis. The clinical characteristics of the remaining 2,713 patients included in the analysis are shown by hyperglycemic status in Table 1.

The sample of n = 2713 had slightly more men (n = 1200, 56%) than women

Table 2. Mortality among study intensive care unit (ICU) patients at the University of Maryland Medical Center, 1996–1998

	Decedents $n = 234$ No. (% total)	Survivors $n = 2479$ No. (% total)
Gender		
Female	107 (8.9)	1093 (91.1)
Male	127 (8.4)	1386 (91.6)
Race[a]		
White	143 (8.2)	1594 (91.8)
Black	86 (10.4)	737 (89.6)
Asian/Hispanic	0 —	10 —
Unknown	5 (3.5)	138 (96.5)
ICU[a]		
Surgical	54 (8.7)	569 (91.3)
Cardiac	37 (6.8)	509 (93.2)
Cardiothoracic	26 (3.5)	720 (96.5)
Neurosurgical	59 (13.1)	393 (86.9)
Medical	58 (16.7)	290 (83.3)
Diabetes history[b]		
No	204 (9.5)	1935 (90.5)
Yes	30 (5.2)	544 (94.8)
Hyperglycemia[b,c]		
No	157 (8.0)	1813 (92.0)
Yes	77 (10.4)	666 (89.6)
Age, yrs, mean (SD)[d]	60.7 (16.4)	57.4 (15.8)
Modified APACHE III, mean (SD)[d,e]	59.9 (27.5)	32.8 (19.6)

APACHE, Acute Physiology and Chronic Health Evaluation.

[a]$p < .05$ for χ^2 test of independence; [b]$p < .05$ for χ^2 test for 2×2 contingency tables; [c]hyperglycemia is defined as glucose >200 mg/dL on the first day of ICU visit; [d]$p < .05$ for Student's t-test of equality of group means; [e]APACHE III was taken from ICU day 1 and modified to exclude glucose points.

with an overall mean age of 57.7 yrs. The majority of patients were white (n = 1737, 64%), with n = 832 (30.3%) black. The CTICU had the largest proportion of patients in the sample with n = 746 (27.5%). There were 234 decedents in the total sample, yielding an in-hospital mortality of 8.6%. The mean glucose was 167.1 (SD = 55.9) mg/dL; 27.4% of the patients had hyperglycemia, as defined by admission glucose >200 mg/dL. Fewer than a quarter of total patients had a history of diabetes (n = 574, 21.2%). The mean modified APACHE III score after subtracting points from blood glucose was 35.1 (SD = 21). Those with hyperglycemia were on average 2.7 yrs older than those without hyperglycemia ($p < .01$). Prevalence of hyperglycemia was significantly higher in females than males (29.9% vs. 25.4%, $p < .01$). There was no significant relation observed between hyperglycemia and race in the study sample. However, there were significant differences among ICU types, with the highest prevalence of hyperglycemia seen in the SICU (36.1%) and the lowest in the MICU (20.1%, $p < .01$). Hyperglycemia was observed in a greater proportion of those with recorded history of diabetes than those without (60.6% vs. 18.5%, $p < .01$). Patients with hyperglycemia were determined to be more ill as measured by APACHE III (44.3 vs. 31.7, $p < .01$) and, accordingly, greater hospital length of stay (12.2 vs. 10.5 days, $p < .01$).

Mortality of the patient population stratified by potential risk factors is shown in Table 2. No significant gender effect was observed. Blacks had a higher mortality rate than whites (10.4% vs. 8.2%, $p < .05$). Across ICUs, the rate of death varied significantly from 3.5% in the CTICU to 16.7% in the MICU. Among those with admission hyperglycemia, 10.4% died, compared with 8.0% of those without hyperglycemia ($p < .05$). The mean modified APACHE III score among those who died was significantly higher than among those who lived (59.9 vs. 32.8, $p < .01$). Those who died were on average 3.3 yrs older than those who lived ($p < .01$).

The overall unadjusted odds ratio (OR) for death by hyperglycemic status was 1.42 (95% confidence interval, 1.09, 1.86). Age had no significant effect on the odds ratio. However, modified APACHE III score was found to be a strong predictor of mortality and a strong confounder of the OR. Each point increase in APACHE III score was found to increase the OR by 0.05 (95% confidence interval, 1.04, 1.05). Both ICU type and diabetes status were found to be effect modifiers of the OR, as determined by the Breslow-Day test ($p < .01$). For example, the APACHE adjusted OR (AOR) among those with diabetes was 0.81 (95% confidence interval, 0.37, 1.77), whereas among those without, the AOR was 1.76 (95% confidence interval, 1.23, 2.53), obviating the combined AOR of 1.27. Similarly, significant heterogeneity of the AOR was seen by ICU type (Breslow-Day $p < .01$), with the most elevated ORs seen in the CICU and NSICU.

The results of the multivariate models are shown after stratification by diabetes history and ICU type in Table 3. In the model unadjusted for APACHE III score, elevated AORs were seen among nondiabetics in the CTICU (2.49 [1.10, 5.64]), CICU (4.02 [1.96, 8.22]), and NSICU (3.42 [1.91, 6.11]). In the model controlling for illness severity using the modified APACHE III, significant elevated ORs for mortality among patients with hyperglycemia but without a history of diabetes were still evident in the CTICU, CICU, and NSICU, although the association was somewhat attenuated. Among diabetics, the presence of hyperglycemia at admission was associated with decreased risk in the MICU (OR 0.23 [0.07, 0.71]), whereas confidence intervals for all other units were not significant. Multivariable models were rerun using an alternate definition of hyperglycemia with a threshold of 150 mg/dL. Results of this analysis were similar to those reported, reflecting the robustness of the findings to the choice of hyperglycemia threshold.

DISCUSSION

We examined the relation between hyperglycemia at admission to the ICU and in-hospital mortality, controlling for severity of illness. We found this association to be modified by type of ICU and by prior history of diabetes, necessitating analysis of the association separately based on ICU type and diabetic status. After adjustment for severity of illness, significantly elevated ORs for mortality associated with admission hyperglycemia were observed in the CICU, CTICU, and NSICU, but only among patients without a history of diabetes. Hyperglycemia was not significantly associated with increased mortality in the medical and surgical units or among patients with a previous history of diabetes.

Table 3. Odds ratio estimates, unadjusted and adjusted by logistic regression, comparing mortality in hyperglycemic[a] to that in normoglycemic patients on admission to the intensive care unit (ICU), by history of diabetes and type of ICU

History of Diabetes	Unit	OR (95% CI)	AOR (95% CI)[b]
No	Medical (n = 304)	0.93 (0.42, 2.03)	0.48 (0.19, 1.16)
	Cardiothoracic (n = 565)	2.49 (1.10, 5.64)	2.84 (1.21, 6.63)
	Cardiac (n = 403)	4.02 (1.96, 8.22)	2.64 (1.14, 6.10)
	Surgical (n = 431)	1.67 (0.91, 3.04)	1.43 (0.72, 2.79)
	Neurosurgical (n = 436)	3.42 (1.91, 6.11)	2.96 (1.51, 5.77)
Yes	Medical (n = 44)	0.39 (0.13, 1.09)	0.23 (0.07, 0.71)
	Cardiothoracic (n = 181)	1.04 (0.36, 2.90)	1.34 (0.45, 3.90)
	Cardiac (n = 143)	1.67 (0.67, 4.09)	1.24 (0.43, 3.52)
	Surgical (n =190)	0.69 (0.29, 1.61)	0.67 (0.26, 1.67)
	Neurosurgical (n = 16)	1.42 (0.53, 3.75)	1.39 (0.47, 4.10)

OR, odds ratio; CI, confidence interval; AOR, adjusted odds ratio.

[a]Hyperglycemia is defined as glucose >200 mg/dL on the first day of ICU visit; [b]AOR adjusted for modified Acute Physiology and Chronic Health Evaluation III, calculated from values on ICU day 1 and not including glucose value.

The relation between glucose levels and mortality among ICU patients has been the subject of previous investigation, although largely in smaller studies that have been unable to consider additional etiological factors (22–25) and/or among study populations with uniform reason for hospital admission (1, 3, 4, 7, 23–27). Our data set included substantial patient numbers from ICUs representing subgroups for which hyperglycemia has been repeatedly shown to be a risk factor, as well as those in which the association is less clear. We observed hyperglycemia to be associated with elevated mortality only in the CICU, CTICU, and NSICU units. Our findings are consistent with previous studies that found an excess risk of mortality associated with hyperglycemia among cardiac and stroke patients. These studies have focused primarily on patients post acute myocardial infarction (3, 10, 23, 26–28) and those post stroke (4, 7, 24, 25, 29, 30). Furthermore, in the large trial by Van den Berghe and colleagues (31), the overall relative risk of 1.7 (comparing the control with treatment group) was largely driven by the more than two-fold relative risk in cardiac surgery patients.

Our data in combination with these studies strongly suggest that the association between hyperglycemia and mortality may not be generalizable to all critically ill patients but only to a subpopulation with vascular disease. The biological mechanism by which elevated blood glucose adversely affects individuals has been extensively reported (12–14, 16, 17, 32). In many cases, these effects may be reasonably expected to disproportionately affect cardiac and neurosurgical patients, as the heart and brain may be target organs in hyperglycemia-induced injury (2, 26, 29).

In our study, we observed statistically significant lower mortality rates in diabetic patients with hyperglycemia in the MICU and generally lower mortality rates among diabetics with hyperglycemia, relative to nondiabetics with hyperglycemia, in other ICUs. These findings are in accord with previous observations. In an observational study of postacute myocardial infarction patients, Wahab and colleagues (3) reported a two-fold increased odds ratio for mortality in hyperglycemic nondiabetic patients, which was higher compared with the risk in diabetic patients. The impact of diabetes has been seen in broader populations as well. Among general ward patients, Umpierrez and colleagues (20) found nearly a five-fold higher risk of in-hospital mortality in patients with newly recognized hyperglycemia at admission compared with those with hyperglycemia and a known history of diabetes. The results of clinical trials further support these epidemiologic observations. The study by Van den Berghe and colleagues (31) included approximately 100 diabetics in both the treatment and control arms. Among diabetics, an overall relative risk of death of 1.4 was found for controls compared with those treated; among nondiabetics, the relative risk was 1.8. The reason critically ill patients with a history of diabetes may not exhibit the same degree of hyperglycemia-associated mortality is not clear. It is possible that patients with a history of diabetes, who exhibited higher admission hyperglycemia, were more likely to receive intensive insulin treatment during their stay.

Capes and colleagues (2, 6) have equated elevated blood glucose at ICU admission with stress hyperglycemia. A link between acute and critical injury and hyperglycemia was recognized as early as the late 19th century (33, 34). The concept of "stress hyperglycemia" has long been observed (34, 35), but its application to many studies in this area is not without ambiguity. Although it is certainly true that individuals entering the ICU are under physiologic stress, it is less clear whether elevated blood glucose at such time may be transient and attributable to stress or simply the continuance of longstanding hyperglycemia. Thus, it has been difficult for epidemiologic studies to determine the difference between acute hyperglycemia and chronic hyperglycemia in relation to health outcomes including in-hospital death.

As a result, although hyperglycemia has been consistently associated with increased mortality rate in certain patient groups, it has not been well established if admission hyperglycemia is a risk factor itself or rather a marker of severity of illness. In the current study, we attempted to address this question by including APACHE III scores in analyses. Among nondiabetics, unadjusted odds ratios for mortality comparing hyperglycemics to normoglycemics were significantly elevated in the CICU, CTICU, and NSICU. After adjustment with the modified APACHE III, point estimates of the risk due to hyperglycemia independent of severity of disease remained statistically significant but were somewhat attenuated. Thus, admission hyperglycemia appeared to have a moderate impact on mortality independent of its role as a marker for severity of illness.

Limitations of the study include the lack of information regarding some informative variables. First, we were unable to distinguish between transient glycemic elevations and previously undiagnosed glucose intolerance or diabetes mellitus. Use of measures such as hemoglobin-A1C may help to differentiate these two groups, but this information was not available in nondiabetics. Additionally, data indicating use of dextrose infusions/parenteral nutrition and/or corticosteroids may have aided in identifying the causes of elevated blood glucose among nondiabetics. We were also lacking information on insulin treatment during the ICU stay. As mentioned previously, it is

The association between hyperglycemia on intensive care unit admission and in-hospital mortality was not uniform in the study population; hyperglycemia was an independent risk factor only in patients without diabetic history in the cardiac, cardiothoracic, and neurosurgical intensive care units.

possible that those with a history of diabetes or those with the highest admission blood glucose levels received more intensive therapy than nondiabetics or those with less severe elevations. This would confer a protective effect to patients with the most severe hyperglycemia and bias results toward the null, potentially making our estimates of risk conservative. Moreover, studies that have included information regarding insulin treatment (9, 31, 36, 37) have had to contend with analytical challenges. The reciprocity of causality that exists for glucose levels and insulin treatment (i.e., high glucose levels lead to insulin treatment, which leads to lower glucose levels, which lead to absence of insulin treatment, etc.) makes their independent effects hard to assess using conventional statistical techniques (38).

CONCLUSIONS

To the best of our knowledge, this is the first study to assess the relation between admission hyperglycemia and in-hospital mortality in different patient populations using ICU type as a proxy for class of medical condition and also to adjust for severity of illness. We found increased mortality among nondiabetics with hyperglycemia in the CICU, CTICU, and NSICU. These findings are significant and suggest that further study is needed to assess whether interventions to target tighter glucose control in these subpopulations without a previous history of diabetes would be beneficial.

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