Journal of Diabetes Science and Technology
Volume 5, Issue 3, May 2011

ORIGINAL ARTICLE

Effect of Diabetes Mellitus on Outcomes of Hyperglycemia in a Mixed Medical Surgical Intensive Care Unit

Andrew T. Schlussel, D.O.,[1] Danielle B. Holt, M.D.,[1] Eric A. Crawley, M.D.,[2] Michael B. Lustik, M.S.,[3] Charles E. Wade, Ph.D,[4] and Catherine F. T. Uyehara, Ph.D.[3]

Abstract

Background:

Intensive insulin therapy and degree of glycemic control in critically ill patients remains controversial, particularly in patients with diabetes mellitus. We hypothesized that diabetic patients who achieved tight glucose control with continuous insulin therapy would have less morbidity and lower mortality than diabetic patients with uncontrolled blood glucose.

Method:

A retrospective chart review was performed on 395 intensive care unit (ICU) patients that included 235 diabetic patients. All patients received an intravenous insulin protocol targeted to a blood glucose (BG) level of 80–140mg/dl. Outcomes were compared between (a) nondiabetic and diabetic patients, (b) diabetic patients with controlled BG levels (80–140mg/dl) versus uncontrolled levels (>140 mg/dl), and (c) diabetic survivors and nonsurvivors.

Results:

Diabetic patients had a shorter ICU stay compared to nondiabetic patients (10 ± 0.7 vs 13 ± 1.1, $p = .01$). The mean BG of the diabetic patients was 25% higher on average in the uncontrolled group than in the controlled (166 ± 26 vs 130 ± 9.4 mg/dl, $p < .01$). There was no difference in ICU and hospital length of stay (LOS) between diabetic patients who were well controlled compared to those who were uncontrolled. Diabetic nonsurvivors had a significantly higher incidence of hypoglycemia (BG <60 mg/dl) compared to diabetic survivors.

Conclusion:

The results showed that a diagnosis of diabetes was not an independent predictor of mortality, and that diabetic patients who were uncontrolled did not have worse outcomes. Diabetic nonsurvivors were associated with a greater amount of hypoglycemic episodes, suggesting these patients may benefit from a more lenient blood glucose protocol.

J Diabetes Sci Technol 2011;5(3):731-740

Author Affiliations: [1]Department of Surgery, Tripler Army Medical Center, Tripler AMC, Hawaii; [2]Department of Pulmonary and Critical Care Medicine, Tripler Army Medical Center, Tripler AMC, Hawaii; and [3]Department of Clinical Investigation, Tripler Army Medical Center, Tripler AMC, Hawaii, [4]Institute of Surgical Research, San Antonio, Texas

Abbreviations: (APACHE) Acute Physiology and Chronic Health Evaluation, (BG) blood glucose, (HbA1c) hemoglobin A1c, (ICU) intensive care unit, (IIT) intensive insulin therapy, (NICE-SUGAR) Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation, (LOS) length of stay, (OR) odds ratio, (SD) standard deviation, (SEM) standard error of the mean, (TAMC) Tripler Army Medical Center

Keywords: blood glucose, diabetes, hyperglycemia, intensive insulin therapy

Corresponding Author: Catherine F. T. Uyehara, Ph.D., Department of Clinical Investigation, 1 Jarrett White Road, Tripler AMC, HI 96859; email address catherine.uyehara@amedd.army.mil

Introduction

There has been considerable interest in the control of blood glucose (BG) in the critically ill ever since the Leuven study in 2001 reported a reduction in mortality with the implementation of intensive insulin therapy (IIT), first in surgical intensive care unit (ICU) patients,[1] and then in medical ICU patients.[2] These studies randomized patients into a conventional treatment group in which a continuous insulin infusion was started only when BG reached 215 mg/dl, versus an intensive treatment group where BG was strictly managed between 80–110 mg/dl.[1,2] The initial surgical ICU study was able to show a reduction in mortality by 32%, and the follow-up medical ICU study showed a 10% reduction in mortality when patients were managed for greater than 3 days. Subsequently, multiple studies have been published debating the benefits of intensive glycemic control. The NICE-SUGAR study[3] has challenged the trend of tight glycemic control in the ICU when patients treated in that study's intensive control group had a 2.6% increase in mortality at 90 days following enrollment.

One of the criticisms of the Leuven studies has been the heterogeneity of the patient population receiving IIT. Research has been directed at identifying specific patient populations that may or may not benefit from IIT. In particular, the role of tight glycemic control in patients with diabetes mellitus remains unclear and has been an area of increasing interest based on published studies.[4–7]

Due to concerns about the benefit versus harm of IIT, data from both Leuven studies were combined to achieve even more statistical power,[8] and the blood glucose was reanalyzed based on tertiles: <110 mg/day, 110–150 mg/day, or >150 mg/day. Interestingly, based on all the groups analyzed, patients with a diagnosis of diabetes mellitus were the only cohort not to demonstrate a survival benefit with IIT. These results were similar to those found by Finney and colleagues,[9] one of the first prospective studies that showed patients with diabetes had neither a significant difference in mortality or hospital length of stay (LOS). Furthermore, results from the NICE-SUGAR study, the largest trial of IIT as of early 2011, also found no associated increased survival in diabetic patients,[3] and this was further supported in a subsequent meta-analysis that included the NICE-SUGAR data.[10]

The purpose of this study was to retrospectively examine the effectiveness and safety of blood glucose control utilizing only continuous insulin therapy in diabetic patients in a mixed medical and surgical ICU. We hypothesized that when the blood glucose of patients with diabetes mellitus is well controlled on continuous insulin, this would result in decreased morbidity and mortality compared to diabetic patients with uncontrolled blood glucose.

Methods

This study was approved by the Human Use and Scientific Review Committees at Tripler Army Medical Center (TAMC). Investigators adhered to the policies for protection of human subjects as prescribed in 45 Code of Federal Regulation 46.

Study Population

A retrospective chart review was performed on all patients admitted to the ICU at TAMC between 2005 to 2009 who received a continuous intravenous insulin infusion (n = 746) according to a standard blood glucose control protocol. Patients were excluded if they were on an insulin infusion for less than 24 hours, had a diagnosis of diabetic ketoacidosis or hyperosmolar nonketotic coma, or if they were less than 18 years old. The 16-bed ICU reflected a community-based practice with both medical and surgical patients.

Description of Tripler Army Medical Center BG Control Protocol

The standard blood glucose management protocol at TAMC is targeted to achieve BG values of 80–140 mg/dl. This standardized protocol target was designed by senior ICU physicians based on evidence of published studies[1–2,12] by using modifications of a known and effective protocol developed from the Yale model for glycemic control.[11] Initiation of this standard protocol was at the discretion of the attending provider. Intravenous insulin dose adjustments were made on an hourly basis with an Excel-based decision support algorithm. Infusion rates were determined based on the rate of change of the BG. Hypoglycemia was defined as a BG less than 60 mg/dl. The value of hypoglycemia was determined during protocol development. There is no agreement on the definition of hypoglycemia, however, one study has shown no further decrease in survival with BG values less than 63 mg/dl; therefore the definition of hypoglycemia remained unchanged for data analysis.[12] If the BG did fall below 60 mg/dl, one ampule of D50

was given and the insulin infusion was held for 1 hour. If nutrition was interrupted, then the infusion rate was decreased by half, and BG values continued to be checked until stabilized or nutrition was restarted.

The majority of the hourly blood glucose samples were from capillary blood samples analyzed by point-of-care testing. The glucometer used in the ICU is the Precision Xceed Pro® from 2008 to present and the Precision PCx was used between 2005 and 2008 (Abbott Laboratories, Abbott Park, Illinois). In addition, venous and arterial blood samples were used to analyze serum glucose with daily serum chemistries and arterial blood gases. The i-STAT 300® (Abbott Laboratories) is the point-of-care device used for measuring arterial blood gases. Venous serum glucometers used by the hospital laboratory include the Roche INTEGRA® from 2007 to 2008 and the Roche Hitachi 917 from 2005 to 2007 (Roche, Basel, Switzerland). The device used for blood glucose testing was based on the nursing staff's discretion. Results from point-of-care devices were not intentionally confirmed with the central laboratory and glucose values were not adjusted for low hematocrit.[13] All glucose values that were used to make insulin adjustments were included in the data analysis. Patients were either NPO (*non per os*) or receiving parenteral or enteral nutrition according to attending physician preference without a standardized nutrition protocol in the ICU.

Data Collection

Baseline demographic, admission diagnoses, and Acute Physiology and Chronic Health Evaluation (APACHE II) scores were collected for all patients at admission. Hourly glucose values and insulin doses were extracted from patient records. For data analysis, patients were categorized into two groups: the controlled BG group, which was defined as patients with mean hourly BG between 80–140 mg/dl, and an uncontrolled BG group, defined as patients with BG ≥141 mg/dl. The diagnosis of diabetes mellitus, either insulin-dependent or noninsulin-dependent, was based on outpatient records and the admission history and physical. Blood glucose variability was determined based on the standard deviation (SD) of the mean hourly glucose values.

Outcome Measures

The primary outcome measure was mortality. Secondary outcomes included hospital and ICU LOS, ventilator days, and readmission to the ICU. The effect of the percentage of time spent at six different ranges of BG values (<80 mg/dl, 81–110 mg/dl, 111–144 mg/dl, 145–180 mg/dl, 181–200 mg/dl, and >200 mg/dl) were evaluated. This value was determined for each patient by dividing the mean BG of each range by the total amount of time (hours) spent in that range. This parameter was used based on a modification of the time-weighted blood glucose analysis used in previous studies.[9] The median values of these ranges were used for statistical comparison. The percent of measurements of BG <60 mg/dl (hypoglycemia) was calculated by dividing the number of BG <60 mg/dl measurements in each patient by the total number of measurements and multiplying by 100. The average of all patients' percentages was looked at across the population. Hypoglycemia was also looked at as what percentage of patients experienced at least one episode of a BG <60 mg/dl.

Statistical Analysis

Data are presented as means ± standard error of the mean (SEM) unless otherwise noted. A p value of less than .05 was considered significant. Student's t-tests were used to compare continuous variables between groups. The Wilcoxon test was used for nonparametric analysis for nonnormally distributed data. Chi square and Fisher's exact tests were used to compare proportional data between groups. Odds ratios (ORs) and confidence intervals (CI) were calculated for risk factors associated with diabetic patients with uncontrolled BG levels. Forward stepwise regression was performed to identify independent variables that were highly correlated with mortality. Multivariate logistic analysis was performed to adjust for covariates and parameter estimates and likelihood ratio tests were generated. Interactions of effects between variables were examined. The logrank test was used to compare Kaplan-Meier survival curves between the two groups. Statistical analyses were performed with the JMP 8.0.7 program (SAS Institute Inc., Cary, NC).

Results

Of the 746 charts reviewed, data from a total of 395 patients who met inclusion criteria were included in the analyses. Of these, 235 (59%) had a documented history of diabetes mellitus and 160 (41%) did not. There were 29 (12%) patients with type 1 diabetes and 206 (88%) with type 2 diabetes. For statistical power, these patients were combined and analyzed as a single group.

Table 1 summarizes demographic, admission-related, and disease history characteristics for diabetic and nondiabetic patients. There was no difference in the percentage of males between groups (78% for diabetic patients vs 76% for nondiabetic patients, p = .54), but diabetic patients

were 8 years older on average than nondiabetic patients (67 ± 0.8 vs 59 ± 1.4, $p < .01$). There was no significant difference between diabetic and nondiabetic patients as to whether the reason for admission was medical or surgical (47 vs 46% medical admissions, respectively, $p = .91$), but of those who had surgical admissions, diabetic patients were more likely than nondiabetic patients to have been admitted for a vascular surgery procedure that required admission to the ICU (8 vs 1%, $p < .01$). **Table 2** compares unadjusted outcomes between diabetic and nondiabetic patients, and shows no differences other than a shorter ICU LOS for diabetic patients (10 ± 0.7 vs 13 ± 1.1, $p = .01$).

The diabetic patients were subdivided based on BG levels into a controlled BG group (BG managed between 80–140 mg/dl in ≥50% of the total measurements) and an uncontrolled BG group (BG ≥141 mg/dl in ≥50% of the total measurements). Patients with a BG value <80 mg/dl were excluded from the portion of the analysis only comparing the controlled and uncontrolled groups based on the design of the protocol, however, these values were analyzed when comparing overall mean BG. **Table 3** compares characteristics between the controlled and uncontrolled groups and shows that the distributions are generally similar except that uncontrolled patients had higher preadmission hemoglobin A1c (HbA1c) values than controlled patients (8.2 ± 0.3 vs 7.3 ± 0.2, $p = .02$).

Table 4 compares the glycemic control variables between diabetic patients with controlled versus uncontrolled BG and shows expected differences due to the study protocol for most variables. Values are expressed as mean ± SD for descriptive purposes. The mean BG was about 25% higher in the uncontrolled BG group than in the controlled BG group (166 vs 130 mg/dl). The mean insulin dose given was also higher for the uncontrolled BG group (4.0 ± 1.5 vs 3.3 ± 1.6 U/hour).

The overall rate of hypoglycemia in diabetic patients was 1%, however, 37% of the diabetic patients studied experienced at least one episode of a BG <60 mg/dl. Patients who were well-controlled had a doubling of hypoglycemic episodes (1.5 vs 0.74%, $p < .01$) as well as a greater rate of single episodes of hypoglycemia (46 vs 33%, $p = .05$) compared to patients in the uncontrolled BG group. The overall rate of low BG values <80 mg/dl was 5.5% with a greater occurrence in the controlled versus uncontrolled group (7.1 vs 4.6%, $p < .01$), and there was no significant association with mortality ($p = .15$). A greater number of diabetic patients with a medical diagnosis had at least one episode of hypoglycemia (45 vs 31%, $p = .03$). This was not statistically greater in the controlled BG group (50 vs 62%, $p = .28$), but occurrence of at least one episode of hypoglycemia in a patient with a medical diagnosis in this group was associated with a higher rate of mortality (46 vs 18%, $p = .01$).

Table 1.
Characteristics of Total Study Population ($n = 395$)

Characteristics	Diabetic patients[a] ($n = 235$)	Nondiabetic patients[a] ($n = 160$)	p
Male sex (%)	184 (78)	121 (76)	.54
Age (year)	67 ± 0.8	59 ± 1.4	<.01
Weight (kg)	88.6 ± 1.8	86.5 ± 1.8	.42
Medical admissions (%)	111 (47)	74 (46)	.91
Surgical admission (%)	124 (53)	86 (54)	
Cardiac surgery (%)	66 (28)	52 (33)	.37
General surgery (%)	29 (12)	19 (12)	.99
Vascular surgery (%)	19 (8)	2 (1)	<.01
Neurosurgery (%)	11 (5)	13 (8)	.20
APACHE II score (%)	19 ± 0.6	18 ± 0.6	.40
History of coronary artery disease (%)	49 (21)	22 (14)	.11
History of renal failure (%)	75 (32)	29 (18)	.31
History of liver disease (%)	11 (5)	10 (6)	.50
Immunocompromised[b] (%)	43 (18)	29 (18)	.89
Steroids (%)	60 (26)	67 (42)	.98
Pneumonia (%)	37 (16)	34 (21)	.18
Vasopressors (%)	210 (90)	144 (91)	.73
Total parenteral nutrition (%)	25 (11)	29 (18)	.04

[a] Values represent mean ± SEM or categorical counts with percentages in parenthesis.
[b] Immunocompromised defined as being on steroids, chemotherapy, or diagnosis of HIV/AIDS.

Table 2.
Outcome Data of Total Population

	Diabetic patients[a] ($n = 235$)	Nondiabetic patients[a] ($n = 70$)	p
Mortality (%)	47 (20)	39 (25)	.32
Readmission rate to ICU[b] (%)	30 (13)	19 (12)	.88
ICU LOS	10 ± 0.7	13 ± 1.1	.01
Hospital LOS	24 ± 1.7	26 ± 2.3	.33
Ventilator days	8 ± 1.3	10 ± 1.5	.21

[a] Values represent number of patients out of total in the subgroup with percentages in parenthesis or mean ± SEM.
[b] Readmission rate defined as at least one readmission per patient.

Among all the patients with diabetes mellitus, there were a total of 165 patients with documented HbA1c within 1 year of hospital admission. The average HbA1c was 7.9%, with a value statistically greater in the uncontrolled versus controlled BG group (8.2 vs 7.3%, $p = .02$). There was no difference in values between medical and surgical patients (8.1 vs 7.6%, $p = .16$) or an association with mortality rate compared to patients who survived (8.0 vs 7.3%, $p = .12$).

Mortality rate was 21% in the controlled BG group compared to 20% in the uncontrolled BG group ($p = .86$) as seen in **Table 5**. Readmission rates to the ICU, LOS in the ICU or hospital, and ventilator days also did not differ significantly between the controlled and uncontrolled BG groups. Based on Kaplan-Meier survivability plots, there was no associated predicted unadjusted mortality based on hospital or total ICU LOS, as depicted in **Figures 1** and **2**.

A forward stepwise regression was performed to identify covariates that predicted mortality (**Table 6**). The base model derived by logistic regression identified age, requirement of mechanical ventilation, medical diagnosis, APACHE II score greater than 18, and diagnosis of sepsis as

Table 3.
Characteristics of Diabetic Study Population ($n = 235$)

Characteristics	Controlled BG group[a] ($n = 82$)	Uncontrolled BG group[a] ($n = 153$)	p
Male sex (%)	66 (82)	118 (77)	.62
Age (year)	65 ± 1.3	68 ± 1.0	.17
Weight (kg)	89 ± 3.3	88 ± 2.0	.88
Medical admissions (%)	36 (44)	74 (48)	.49
Surgical admission (%)	46 (56)	78 (51)	
Cardiac surgery (%)	23 (28)	43 (28)	.99
General surgery (%)	13 (16)	16 (10)	.30
Vascular surgery (%)	6 (7)	13 (8)	.80
Neurosurgery (%)	4 (5)	7 (5)	.99
HbA1c (%) ($n = 165$)	7.3 ± 0.2	8.2 ± 0.3	.02
APACHE II score (%)	19 ± 0.9	19 ± 0.7	.81
APACHE II score >18	35%	64%	<.01
History of CAD[b] (%)	15 (18)	34 (22)	.61
History of renal failure (%)	28 (34)	58 (38)	.66
History of liver disease (%)	4 (5)	7 (5)	.99
Immunocompromised[b] (%)	15 (18)	28 (18)	.99
Steroids (%)	23 (28)	37 (24)	.53
Pneumonia (%)	14 (17)	23 (15)	.70
Vasopressors (%)	77 (94)	133 (88)	.24
Total parenteral nutrition (%)	11 (13)	14 (9)	.40

[a] Values represent mean ± SEM or categorical counts with percentages in parenthesis.
[b] Immunocompromised defined as being on steroids, chemotherapy, or diagnosis of HIV/AIDS. CAD, coronary artery disease

Table 4.
Effectiveness of Glycemic Control in Diabetic patients

	Controlled BG group[a] ($n = 82$)	Uncontrolled BG group[a] ($n = 153$)
Measurements in protocol range (%)	59 ± 15	38 ± 15
Measurements >141 mg/dl (%)	36 ± 20	58 ± 17
Measurements <80 mg/dl (%)	7.1 ± 5.5	4.6 ± 3.9
Measurements <60 mg/dl (%)	1.5 ± 2.6	0.74 ± 1.5
Mean number of BG measurements	111 ± 140	103 ± 176
Admission BG (mg/dl)	168 ± 101	212 ± 194
Time on insulin drip (day)	4.8 ± 6.2	4.0 ± 6.0
Mean BG (mg/dl)	130 ± 9.4	166 ± 26
Standard deviation BG	43 ± 11	64 ± 26
Maximum BG (mg/dl)	274 ± 98	353 ± 166
Minimum BG (mg/dl)	61 ± 17	69 ± 25
Mean insulin (U/hour)	3.3 ± 1.6	4 ± 1.5
Standard deviation of insulin	1.9 ± 1.4	2.3 ± 1.5
Maximum insulin (U/hour)	8.9 ± 6.6	11 ± 8.3

[a] Values represent mean ± SD.

Table 5.
Outcomes of Diabetic patients on Continuous Insulin Therapy

	Controlled BG group[a] ($n = 82$)	Uncontrolled BG group[a] ($n = 153$)	p
Mortality (%)	17 (21)	30 (20)	.86
Readmission rate to ICU[b] (%)	9 (11)	21 (14)	.68
ICU LOS	10 ± 1.2	10 ± 0.8	.65
Hospital LOS	22 ± 2.5	24 ± 2.3	.59
Ventilator days	7 ± 1.1	8.8 ± 1.8	.40

[a] Values represent number of patients out of total in the subgroup with percentages in parenthesis or mean ± SEM.
[b] Readmission rate defined as at least one readmission per patient.

contributing predictors of mortality. Independent variables that influenced blood glucose control were individually entered into the model. There was no association between increased mortality in diabetic patients with uncontrolled BG, those with higher mean hourly BG measurements or BG variability, or greater admission glucose values (**Figure 3**). There was also no increased mortality in patients requiring a higher mean insulin dose.

Subgroup analysis was performed comparing diabetic survivors and nonsurvivors. The overall mortality rate of the diabetic patient population that received continuous insulin was 20%. When evaluating diabetic nonsurvivors, these patients had a greater adjusted rate of at least one episode of hypoglycemia when compared to survivors [OR 2.3, 95% confidence interval (CI) 1.0–5.4; $p = .05$). Furthermore, nonsurvivors required mechanical ventilation for a longer period of time and remained in the ICU for more than twice the amount of time as diabetic patients who survived (**Table 7**).

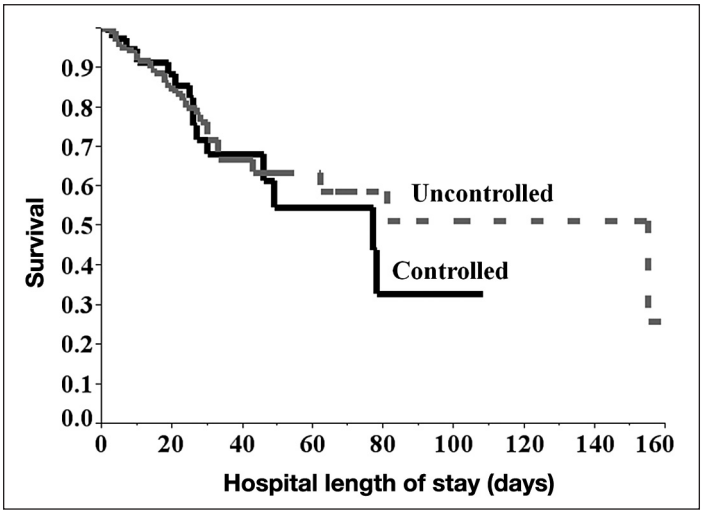

Figure 1. Comparison of survival curves based on hospital LOS in diabetic patients. Kaplan-Meier survivability plot shows no difference in relationship of mortality and hospital LOS between diabetic patients with controlled or uncontrolled blood glucose ($p = .70$).

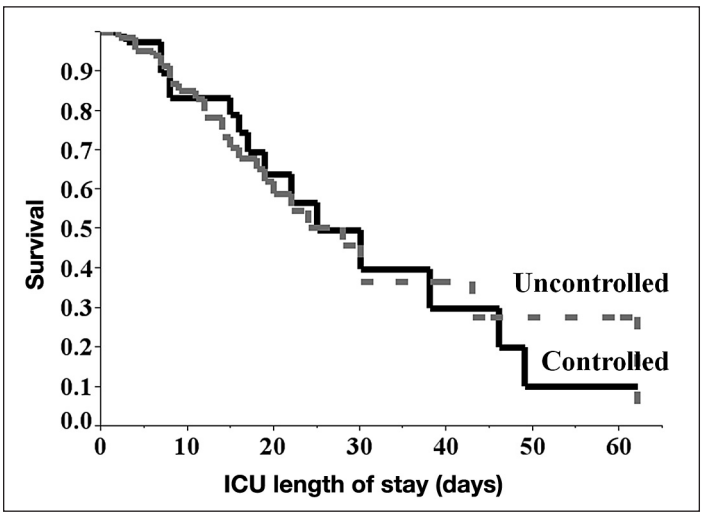

Figure 2. Comparison of survival curves based on ICU LOS in diabetic patients. Kaplan-Meier survivability plot shows no difference in relationship of mortality and ICU LOS between diabetic patients with controlled or uncontrolled blood glucose ($p = .86$).

The effect of the percentage of time spent within BG intervals was analyzed. Six ranges of BG levels were compared as seen in **Figure 4**, and the mean values

Table 6.
Factors Included in Forward Stepwise Regression Analyses to Predict Mortality

Age	Sex	Readmission rate to the ICU
Mechanical ventilation	Medical diagnosis	BG <60 mg/dl
Steroids	Immunocompromised	Use of vasopressors
Admission BG (mg/dl)	Weight (kg)	History of coronary artery disease
Chronic kidney disease stage V	History of liver failure	Wound infection
Diagnosis of pneumonia	Total parenteral nutrition	

Table 7.
Mortality Analysis of Patients with Diabetes

	Diabetes survivors[a] ($n = 188$)	Diabetic nonsurvivors[a] ($n = 47$)	p
Measurements in protocol range (%)	46 ± 1.3	44 ± 2.6	.69
One event of hypoglycemia[b] (%)	58 (31)	30 (64)	<.01
Mean BG (mg/dl)	153 ± 2.0	156 ± 3.7	.58
Maximum BG (mg/dl)	321 ± 11	343 ± 22	.37
Minimum BG (mg/dl)	68 ± 1.6	57 ± 3.3	<.01
Standard deviation BG	56 ± 1.8	60 ± 3.1	.36
Mean Insulin (U/hour)	3.7 ± 0.1	3.9 ± 0.2	.68
Standard deviation of insulin	2.1 ± 0.1	2.3 ± 0.2	.29
Readmission rate to ICU	20 (11)	10 (21)	.08
ICU LOS	8.3 ± 0.7	17 ± 2.0	<.01
Hospital LOS	23 ± 1.9	26 ± 4.0	.52
Ventilator days	5.3 ± 1.1	19 ± 3.9	<.01

[a] Values represent mean ± SEM or categorical counts with percentages in parenthesis.
[b] Hypoglycemia defined as BG <60 mg/dl.

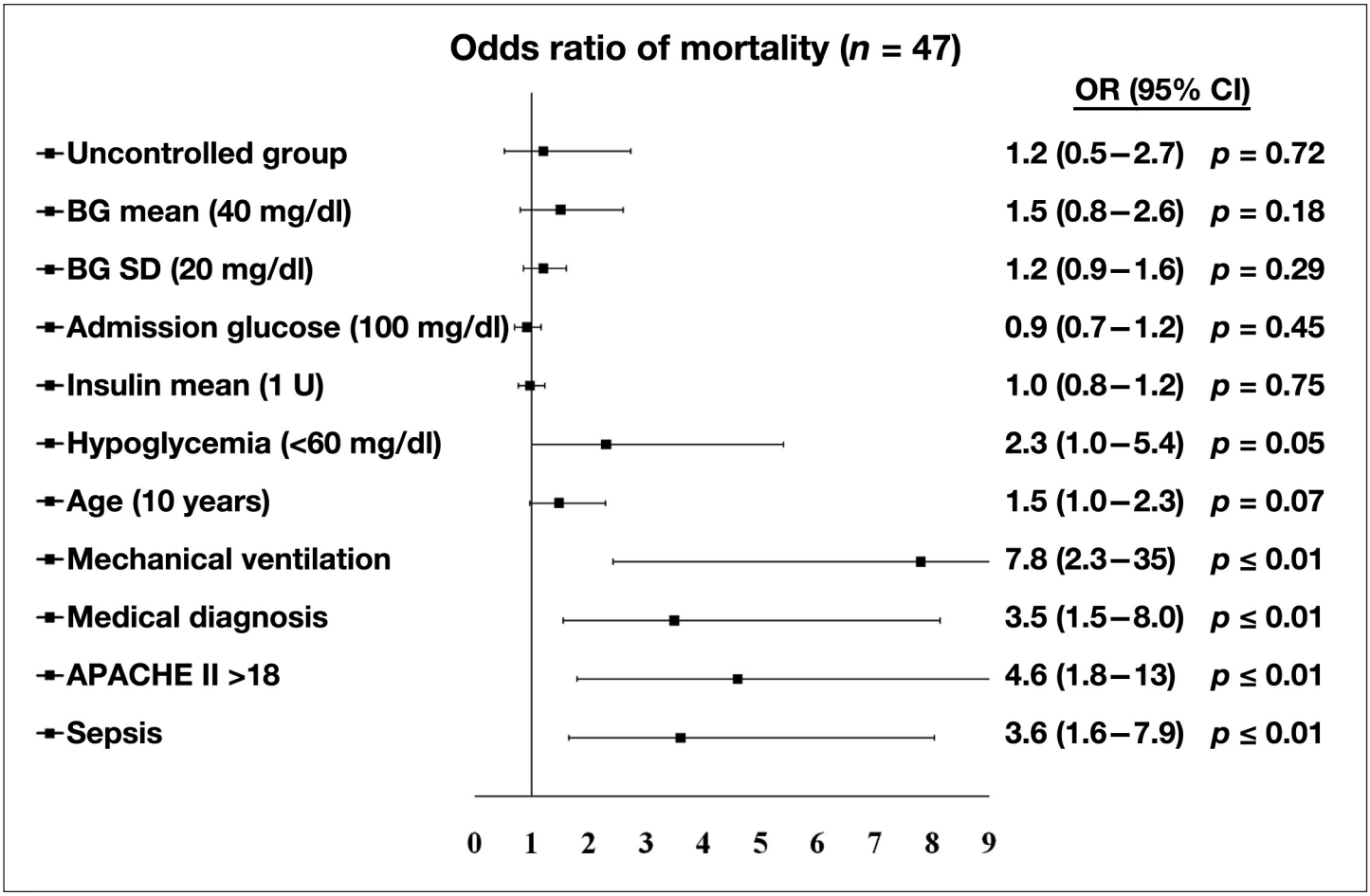

Figure 3. Adjusted odds ratio for predictors of mortality. The base model included age adjusted for every 10 years, requirement of mechanical ventilation, nonsurgical (medical) admission diagnosis, APACHE II score ≥18, and diagnosis of sepsis. All other independent variables were entered into the model individually in stepwise regression.

as well as median values of each group were used for analysis. There was no significant association with mortality among the subgroups.

Discussion

Patients with diabetes mellitus are a unique population. There are multiple studies performed in the outpatient setting that demonstrate the complications imposed on these patients from the long-term effects of chronic hyperglycemia.[14–19] These studies clearly show that these patients are at higher risk for nephropathy, neuropathy, cardiovascular disease, and death. Experimental studies involving humans, animal, and cell cultures have identified an impairment of polymorphonuclear cells to perform their appropriate function, i.e., chemotaxis and phagocytosis.[20–26] Other studies have identified an inappropriate rise in cytokines in diabetic patients with hyperglycemia as well as inducing a procoagulant state during severe illness.[24] Together, this alteration of

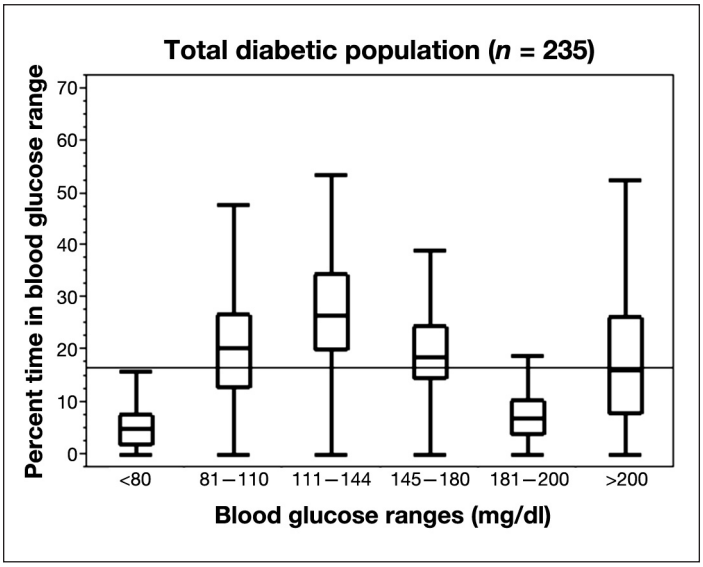

Figure 4. Percent of time spent in blood glucose ranges during the course of continuous insulin therapy. Values represent the number of hours recorded in the blood glucose range divided by the total amount of hours on continuous insulin therapy.

the inflammatory response places diabetic patients at a higher risk of developing life-threatening infections.[20] Interestingly, these effects of chronic hyperglycemia are potentially a risk modifier once these patients develop sepsis and are admitted to the ICU. Some studies have demonstrated diabetic patients with sepsis are actually at a lower risk for developing acute lung injury and have an overall lower mortality rate, possibly due to their impaired neutrophil and inflammatory response.[20–22]

Diabetic patients were on average older and received a significantly greater number of vascular surgeries then nondiabetic patients, which was expected. Diabetes and a nonsurgical admission diagnosis foretold a worse outcome in patients based on the logistic regression model. In a published meta-analysis, it was found that the only patients who benefited from IIT were those who required surgery.[10] Although the number of diabetic patients per surgical group in this study was small, these results warrant further investigation to evaluate the effects of stress-induced hyperglycemia solely in diabetic patients in the perioperative setting.

The effects of hyperglycemia may portend a different biological or clinical implication in critically ill patients with diabetes mellitus. Other studies have shown no association between hyperglycemia and ICU LOS or mortality and even a lower odds ratio for death at any level of hyperglycemia.[4] This perhaps indicates that hyperglycemia control is a long-term health issue and may not influence outcomes of acute patient management during ICU stays. The diabetic patients analyzed in our study had a significantly lower ICU LOS compared to the nondiabetic patients, again suggesting that diabetic patients may not require as strict an insulin protocol.

It has been reported that diabetic patients have no increased risk of mortality and that a diagnosis of diabetes mellitus may actually be a marker for decreased mortality in the ICU.[5] Hyperglycemia in patients with diabetes in the ICU may not be as significant a marker of systemic illness as in nondiabetic patients, and the degree of glycemic control needed in all patients has yet to be clearly defined. These findings are further substantiated in a study by Egi and colleagues[6] that showed an association with a greater time-weighted BG value with a higher pre-admission HbA1c. In our study, although diabetic patients with poor blood glucose control had higher preadmission HbA1c values, this did not appear to be associated with increased morbidity or mortality, in accordance with these other studies evaluating the effects of hyperglycemia in diabetic patients.

Hypoglycemia is known to cause serious complications, from sweating and confusion to seizures and death, and even mild to moderate hypoglycemia is an independent predictor of in-hospital mortality.[1,12,27] Although a specific value to define hypoglycemia has not been published, studies have described it from as low as <40 mg/dl to as high as <80 mg/dl. Based on the design of our institution's insulin protocol, hypoglycemia was defined to be levels less than 60 mg/dl. The demarcation of 60 mg/dl appears to be appropriate when reviewing the rate of mortality reported at values less than 60 mg/dl.[12] The overall hypoglycemia rate in our study appears to be comparable if not lower than those found in the Leuven and NICE-SUGAR studies,[1,3] however, this comparison can only be cautiously suggested as hypoglycemia was defined as a BG <40 mg/dl in these studies. In this study, all episodes of hypoglycemia were assumed to be a result of insulin administration, as this study only evaluated patients receiving a continuous infusion of insulin. Although the rate of overall hypoglycemic measurements per person was low, diabetic patients experienced at least one hypoglycemic episode 37% of the time. A higher rate of hypoglycemia in the controlled group compared to the uncontrolled group was associated with higher mortality. The high rate of a single episode of hypoglycemia may be a function of the protocol itself or a marker of disease severity in these patients.[12] The need to carefully monitor for hypoglycemia, possibly with continuous glucose monitors, especially in diabetic patients, has been indicated in other studies that show that severe hypoglycemia is a strong predictor of mortality in these patients even if they have only suffered from one episode of hypoglycemia.[12,27]

Hyperglycemia and fluctuations in blood glucose (after adjusting for other significant predictors of mortality) were not associated with mortality in diabetic patients.[5,7] This finding may be associated with nonbiologic reasons indicated in other studies, more attentive care by providers, earlier presentation to a health care provider for acute illnesses, appropriate treatment of other comorbidities, as well as healthier lifestyle recommendations provided via counseling to outpatients.[5,20] In contrast to hyperglycemia, this data demonstrates that during acute illness, diabetic patients are intolerant of *hypo*glycemia, even if an event only occurs once in their ICU course.[5] Furthermore, it may also be the rapid normalization to what is thought to be euglycemia that could be potentially deleterious to these patients.[6,8] This study was unable to determine the rate at which target blood glucose was achieved and this warrants further investigation in patients with diabetes.

There are multiple limitations to this study design. First, this is an observational study and therefore could only evaluate associations with hyper- and hypoglycemia and death, and not causality.[28] The small sample size makes achieving statistical power difficult; however, this study has a significant number of data points per patient with an average of over 100 measurements in both the controlled and uncontrolled BG groups. Various devices were utilized to calculate BG measurements and were not confirmed with central laboratory assays in a standard fashion. It has also been established that point-of-care devices have significant error rates in the face of a low hematocrit, which was not corrected for in this study.[13] Nonetheless, each value that was used to make a clinical decision was included in the analysis, which is reflective of clinical practice.

There are inherent weaknesses in evaluating an insulin infusion protocol as there is not one model that has become standard of care. The insulin treatment protocol utilized at our institution included modifications of a published and effective algorithm.[11] but there are many factors in the ICU that may require deviation from the protocol, and these were unable to be accounted for in this retrospective chart review. Complete nutritional data was unknown for all patients, and it would be important in future studies to identify a clear correlation with caloric intake and glycemic control, which has been done in other studies.[1–2] Finally, this was a retrospective review over multiple years and the patient medical records were not always equivalent. This was apparent when evaluating HbA1c levels as all diabetic patients did not have up-to-date values available (**Table 3**), and although a statistical significance was obtained, further clinical relevance might have been unmasked if a larger data collection could have been performed.

Conclusion

In conclusion, the results show that a diagnosis of diabetes mellitus is not an independent predictor of mortality in this patient population, and that diabetic patients on continuous insulin therapy who have uncontrolled BG did not have worse outcomes. Diabetic nonsurvivors were associated with a greater amount of hypoglycemic episodes and lower minimum BG levels. This suggests that these patients may benefit from a more lenient blood glucose protocol (BG range of 140–180 mg/dl), as now recommended by the American Diabetes Association during critical illness.[29] Avoidance of episodes of hypoglycemia may be more important than achieving tight BG control in diabetic patients. Further prospective, randomized studies are needed to fully elucidate the effects of specific glycemic control targets in critically ill patients with diabetes.

Disclaimer:

The views expressed in this paper are those of the authors and do not reflect the official policy or position of the Department of the Army, Department of Defense, or the U.S. Government.

Funding:

This project was supported by the Technologies for Metabolic Monitoring and Julia Weaver Fund, a congressionally directed program jointly managed by the United States Army Medical Research and Materiel Command, National Institutes of Health, National Aeronautics and Space Administration, Juvenile Diabetes Research Foundation, and Combat Casualty Care Division (United States Army Medical Research and Materiel Command).

Acknowledgments:

The authors are grateful for the contributions of Sheila Sherlock in assisting with data collection.

References:

1. Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R. Intensive insulin therapy in the critically ill patients. N Engl J Med. 2001;345(19):1359-67.
2. Van den Berghe G, Wilmer A, Hermans G, Meersseman W, Wouters P, Milants Ilse, Van Wijngaerden E, Bobbaers H, Bouillon R. Intensive insulin therapy in the medical ICU. N Engl J Med. 2006;354(5):449-61.
3. Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, Bellomo R, Cook D, Dodek P, Henderson WR, Hébert PC, Heritier S, Heyland DK, McArthur C, McDonald E, Mitchell I, Myburgh JA, Norton R, Potter J, Robinson BG, Ronco JJ. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009;360(13):1283-97.
4. Egi M, Bellomo R, Stachowski E, French CJ, Hart GK, Hegarty C, Bailey M. Blood glucose concentration and outcome of critical illness: the impact of diabetes. Crit Care Med. 2008;36(8):2249-55.
5. Graham BB, Keniston A, Gajic O, Trillo Alvarez CA, Medvedev S, Douglas IS. Diabetes mellitus does not adversely affect outcomes from a critical illness. Crit Care Med. 2010;38(1):16-24.
6. Egi M, Bellomo R, Stachowski E, French C, Hart G, Taori G, Hegarty C, Bailey M. The interaction of chronic and acute glycemia with mortality in critically ill patients with diabetes. Crit Care Med. 2011;39(1):105-11.

7. Krinsley JS. Glycemic variability and mortality in critically ill patients: the impact of diabetes. J Diabetes Sci Technol. 2009;3(6):1292-301.

8. Van den Berghe G, Wilmer A, Milants I, Wouters P, Bouckaert B, Bruyninckx F, Bouillon R, Schetz M. Intensive insulin therapy in mixed medical/surgical intensive care units: benefit versus harm. Diabetes. 2006;55(11):3151-9.

9. Finney SJ, Zekveld C, Elia A, Evans TW. Glucose control and mortality in critically ill patients. JAMA. 2003;290(15):2041-7.

10. Griesdale DE, de Souza RJ, van Dam RM, Heyland DK, Cook DJ, Malhotra A, Dhaliwal R, Henderson WR, Chittock DR, Finfer S, Talmor D. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. CMAJ. 2009;180(8):821-7.

11. Goldberg PA, Siegel MD, Sherwin RS, Halickman JI, Lee M, Bailey VA, Lee SL, Dziura JD, Inzucchi SE. Implementation of a safe and effective insulin infusion protocol in a medical ICU. Diabetes Care. 2004;27(2):461-7.

12. Egi M, Bellomo R, Stachowski E, French CJ, Hart GK, Taori G, Hegarty C, Bailey M. Hypoglycemia and outcome in critically ill patients. Mayo Clin Proc. 2010;85(3):217-24.

13. Mann EA, Salinas J, Pidoke HF, Wolf SE, Holcomb JB, Wade CE. Error rates resulting from anemia can be corrected in multiple commonly used point-of-care glucometers. J Trauma. 2008;64(1):15-21.

14. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329(14):977-86.

15. Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F, Grimm RH Jr, Probstfield JL, Simons-Morton DG, Friedewald WT. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008;358(24):2545-59.

16. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven P, Zieve FJ, Marks J, Davis SN, Hayward R, Warren SR, Goldman S, McCarren M, Vitek ME, Henderson WG, Huang GD. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med. 2009;360(2):129-39.

17. Pirart J. Diabetes mellitus and its degenerative complications: a prospective study of 4,400 patients observed between 1947 and 1973. Diabetes Metab. 1977;3(2):97-107. French.

18. Skyler JS. Diabetic complications. The importance of glucose control. Endocrinol Metab Clin North Am. 1996;25(2):243-54.

19. Fox CS, Coady S, Sorlie PD, D'Agostino RB Sr, Pencina MJ, Vasan RS, Meigs JB, Levy D, Savage PJ. Increasing cardiovascular disease burden due to diabetes mellitus: the Framingham Heart Study. Circulation. 2007;115(12):1544-50.

20. Esper AM, Moss M, Martin GS. The effect of diabetes mellitus on organ dysfunction with sepsis: an epidemiological study. Crit Care. 2009;13(1):R18.

21. Stegenga M, Vincent J, Vail G, Xie J, Haney D, Williams M, Bernard GR, van der Poll T. Diabetes does not alter mortality or hemostatic and inflammatory responses in patients with severe sepsis. Crit Care Med. 2010;38(2):539-545.

22. Moss M, Guidot DM, Steinberg KP, Duhon GF, Treece P, Wolken R, Hudson LD, Parsons PE. Diabetic patients have a decreased incidence of acute respiratory distress syndrome. Crit Care Med. 2000;28(7):2187-92.

23. Monnier L, Mas E, Ginet C, Michel F, Villon L, Cristol JP, Colette C. Activation of oxidation by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. JAMA. 2006;295(14):1681-7.

24. Stegenga ME, van der Crabben SN, Blümer RM, Levi M, Meijers JC, Serlie MJ, Tanck MW, Sauerwein HP, van der Poll T. Hyperglycemia enchances coagulation and reduces neutrophil degranulation, whereas hyperinsulinemia inhibits fibrinolysis during human endotoxemia. Blood. 2008;112(1):82-9.

25. Morigi M, Angioletti S, Imberti B, Donadelli R, Micheletti G, Figliuzzi M, Remuzzi A, Zoja C, Remuzzi G. Leukocyte-endothelial interaction is augmented by high glucose concentrations and hyperglycemia in a NF-kB-dependent fashion. J Clin Invest. 1998;101(9):1905-15.

26. Klip A, Tsakiridis T, Marette A, Ortiz PA. Regulation of expression of glucose transporters by glucose: a review of studies *in vivo* and in cell cultures. FASEB J. 1994;8(1):43-53.

27. Krinsley JS, Grover A. Severe hypoglycemia in critically ill patients: risk factors and outcomes. Crit Care Med. 2007;35(10):2262-7.

28. Falciglia M, Freyberg RW, Almenoff PL, D'Alessio DA, Render ML. Hyperglycemia-related mortality in critically ill patients varies with admission diagnosis. Crit Care Med. 2009;37(12):3001-9.

29. American Diabetes Association. Standards of medical care in diabetes—2010. Diabetes Care. 2010;33(Suppl 1):S11-61.