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Diabetes Is Not Associated With Increased Mortality in Emergency Department Patients With Sepsis

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Abstract

Study objective—Despite its high prevalence, the influence of diabetes on outcomes of emergency department (ED) patients with sepsis remains undefined. Our aim is to investigate the association of diabetes and initial glucose level with mortality in patients with suspected infection from the ED.

Methods—Three independent, observational, prospective cohorts from 2 large US tertiary care centers were studied. We included patients admitted to the hospital from the ED with suspected infection. We investigated the association of diabetes and in-hospital mortality within each cohort separately and then overall with logistic regression and generalized estimating equations adjusted for age, sex, disease severity, and sepsis syndrome. We also tested for an interaction between diabetes and hyperglycemia/hypoglycemia.

Results—A total of 7,754 patients were included. The mortality rate was 4.3% (95% confidence interval [CI] 3.9% to 4.8%) and similar in diabetic and nondiabetic patients (4.1% versus 4.4%; absolute risk difference 0.4%; 95% CI –0.7% to 1.4%). There was no significant association between diabetes and mortality in adjusted analysis (odds ratio [OR] overall 0.85; 95% CI 0.71 to 1.01). Diabetes significantly modified the effect of hyperglycemia and hypoglycemia with mortality; initial glucose levels greater than 200 mg/dL were associated with higher mortality in nondiabetic patients (OR 2.1; 95% CI 1.4 to 3.0) but not in diabetic patients (OR 1.0; 95% CI 0.2 to 4.7), whereas glucose levels less than 100 mg/dL were associated with higher mortality mainly in the diabetic population (OR 2.3; 95% CI 1.6 to 3.3) and to a lesser extent in nondiabetic patients (OR 1.1; 95% CI 1.03 to 1.14).

Conclusion—We found no evidence for a harmful association of diabetes and mortality in patients across different sepsis severities. High initial glucose levels were associated with adverse outcomes in the nondiabetic population only. Further investigation is warranted to determine the mechanism for these effects.

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INTRODUCTION

Among patients with severe sepsis, 20% to 30% are reported to have diabetes, yet the exact influence of diabetes on sepsis outcomes remains unclear.¹⁻⁶ Preclinical studies have suggested that diabetes interacts with different components of the innate immune system in vitro, such as chemotaxis, phagocytosis, and activation of neutrophils and macrophages.^{7,8} In addition, diabetes has been shown to have direct inhibitory effects on the adaptive immune system, namely, on the function of T lymphocytes, immunoglobulins, and complement.^{9,10} Animal diabetes models provide evidence that hyperglycemia is associated with decreased bacterial clearance, possibly contributing to higher mortality among diabetic animals in sepsis experiments.¹¹ Clinical studies, however, investigating the influence of diabetes on sepsis-related mortality have shown mixed results.¹² Some trials report higher mortality rates among diabetic patients,¹³⁻²⁰ whereas others reported no association for diabetes and mortality.^{1,21-24} Indeed, a third group of studies found a rather protective effect of diabetes during sepsis.²⁵⁻²⁸

As a limitation, most of these previous clinical studies were either large population-based trials based on data from national registries or limited to only critically ill patients from the ICU setting. Clinical data from the most proximal part of the hospital presentation, the emergency department (ED) setting, and across sepsis severities are largely lacking. The aim of this analysis was to investigate the association of diabetes and hyperglycemia with mortality in 3 temporally or geographically distinct cohorts of patients with a suspected infection and who were admitted to the hospital from the ED.

MATERIALS AND METHODS

Setting and Study Design

For this analysis, we used data from 3 temporally or geographically distinct, prospectively collected, observational cohort studies of patients with clinically suspected infection and who were admitted to the hospital from the EDs at 2 medical centers. The first 2 cohorts were assembled at the Beth Israel Deaconess Medical Center Medical Center (BIDMC), a 600-bed urban tertiary care center in Boston, MA, with approximately 50,000 ED visits per year, between December 10, 2003 and September 30, 2004, with the primary objective of assessing the performance of serum lactate as a risk prognostication tool in sepsis.^{29,30} The second cohort was also collected at BIDMC between September 16, 2005, and September 30, 2006, as part of a study whose primary objective was to examine the utility of point-of-care lactate assessment.³¹ The third cohort was assembled between January 6, 2004, and January 6, 2005, at Carolinas Medical Center in Charlotte, NC, an 800-bed teaching and tertiary referral hospital with greater than 100,000 patient visits per year. The primary objective of this study was to assess the prognostic significance of hypotension in ED patients.³² The studies were approved by the institutional review board at BIDMC and the institutional review board and privacy board at Carolinas Healthcare System, respectively, which granted waiver of informed consent. All 3 studies are in compliance with the Helsinki Declaration.

Selection of Participants and Data Collection and Processing

All 3 cohorts were prospectively enrolled with similar inclusion criteria, as described below. All 3 cohorts were stratified for sepsis severity, disease severity, and glucose measurements according to ED chart abstraction alone. For the first 2 BIDMC cohorts, inclusion criteria were adult age (18 years or older) and clinically suspected infection, as indicated by an admitting diagnosis and a confirmatory chart review. The detailed methodology is reported elsewhere.^{30,32} Briefly, trained research assistants reviewed the daily ED log for an

admission diagnosis consistent with infection (ie, pneumonia) or possibly infection related (ie, shortness of breath) to identify patients. Interrater reliability for this approach was excellent (Cohen's $\kappa=0.9$) and has been previously reported.²⁹ All records of patients with infection or possible infection underwent a confirmatory review to affirm a suspicion of infection according to ED presentation as documented in the medical decisionmaking portion of the chart. Patients were judged to have a clinically suspected infection if they met any of the following criteria: (1) a documented source of infection such as a pneumonia on a chest radiograph, greater than 5 WBCs in the urine, intra-abdominal infection on computed tomography scan, etc; (2) a documentation of infection by the clinician in the medical decisionmaking portion of the chart; or (3) administration of antibiotics in the ED. Chart abstraction occurred in accordance with ED information only and without any subsequent knowledge of the hospital course.

Inclusion criteria for the third Carolinas Medical center cohort were age 18 years or older, admission to the hospital from the ED, and suspected infection. The identification of patients with suspected infection was determined by selecting patients who received antibiotics in the ED. Patients were sampled with a standard random sampling methodology that allowed the enrollment of a representative population of subjects during the 1-year enrollment period, as previously described.³² Enrollment took place during random 24-hour periods, chosen from a standard random sample of 24-hour periods (12 AM to 11:59 PM), comprising half of the number of days in each block.

Outcome Measures

Patients were classified as having preexisting diabetes by either self-report or documentation in their medical record. Initial blood glucose levels on ED admission were recorded. Glycosylated hemoglobin (HbA1C) or islet antibody levels were not routinely measured as part of the ED evaluation, so they were not assessed to confirm the diagnosis of diabetes. Sepsis syndrome consisted of the following categories: sepsis, severe sepsis, and septic shock based on an adapted version of international criteria.^{4,33} Disease severity was assessed with the Mortality in Emergency Department Sepsis score and the Simplified Acute Physiology Score II³⁴ for the third cohort. The primary endpoint for this analysis was all-cause in-hospital mortality, defined as not surviving to hospital discharge.

Primary Data Analysis

First, we used descriptive statistics, including mean with SD and frequencies to describe the populations, as appropriate. Next, we investigated the association of diabetes and mortality in logistic regression analysis and report odds ratios (ORs) and 95% confidence intervals (CIs). We first calculated an analysis adjusted for age, sex, disease severity, and sepsis syndrome for all 3 independent cohorts. Model fit was assessed with Hosmer-Lemeshow goodness-of-fit tests. To combine the findings from the 3 cohorts, we performed hierarchic modeling with a generalized estimating equation, using exchangeable variance–covariance structure with compound symmetry. We also analyzed the association between hyperglycemia (serum glucose level >200 mg/dL) and low glucose levels (serum glucose level <100 mg/dL) and mortality, both stratified by diabetes status and as part of a generalized estimating equation with an interaction term. For the generalized estimating equation, we included hyperglycemia, hypoglycemia, the interaction between diabetes and hyperglycemia/hypoglycemia, and an adjustment for age, sex, sepsis syndrome, and sepsis severity.

All reported CIs are 2-sided 95% intervals, and tests were performed at the 2-sided 5% significance level. All analyses were performed with SAS (version 9.2; SAS Institute, Inc., Cary, NC).

RESULTS

Characteristics of Study Subjects

Overall, 7,754 patients from 3 prospective patient cohorts are included in this analysis ($n=2,132$, $n=4,618$, and $n=1,004$ in cohorts 1, 2, and 3, respectively). A total of 57.5% of patients had sepsis, 37% had severe sepsis, and 5.5% had septic shock, with a relatively even distribution in the cohorts. The mean age of patients ranged from 54 to 60 years, and between 48% and 52% were men (Table). There was a high burden of comorbidities in all 3 cohorts, and diabetes was present in 27% (95% CI 25% to 28%), 23% (95% CI 21% to 24%), and 24% (95% CI 21% to 26%) of patients within the 3 cohorts. More detailed patient characteristics overall and within the 3 cohorts are presented in the Table.

The mortality rate overall was 4.3% (95% CI 3.9% to 4.8%) and ranged between 3.9% (95% CI 3.1% to 4.7%) and 6.1% (95% CI 4.6% to 7.6%). Mortality was lowest in patients with sepsis (1.1%; 95% CI 0.1% to 1.4%) and increased to 6.7% (95% CI 5.8% to 7.6%) in patients with severe sepsis and 22.8% (95% CI 18.8% to 26.8%) in patients with septic shock. There was no difference in the mortality rate between diabetic and nondiabetic patients overall (4.1% versus 4.4%; absolute risk difference 0.4%; 95% CI -0.7% to 1.4%), with no difference found in any individual cohort. We further assessed the association of diabetes and mortality in logistic regression analyses adjusted for age, sex, disease severity, and sepsis syndrome. Hosmer-Lemeshow goodness-of-fit tests of the models showed no evidence for model miscalibration ($P>.05$ for all tests). There was no significant association between diabetes and mortality in any of the 3 cohorts, with OR ranging from 0.66 (95% CI 0.37 to 1.17) to 0.96 (95% CI 0.67 to 1.38) (Figure 1). In the overall hierarchic model, there was again no harmful association between diabetes and mortality (OR 0.85; 95% CI 0.71 to 1.01).

To investigate the influence of initial glucose levels on mortality stratified by preexisting diabetes, we first calculated crude mortality rates in patients with and without diabetes and with low (<100 mg/dL), intermediate (100 to 200 mg/dL), and high (>200 mg/dL) glucose levels (Figure 2). Nondiabetic patients with glucose levels greater than 200 mg/dL had significantly higher mortality in all 3 cohorts and in the overall model compared with diabetic patients. Conversely, diabetic patients with glucose levels less than 100 mg/dL had significantly higher mortality rates compared with nondiabetic patients overall and in cohort 2.

The influence of preexisting diabetes on the association of initial glucose levels and mortality was further tested by inclusion of an interaction term between glucose range and diabetes in our multivariate model (Figure 3). We found evidence for effect modification for both high and low glucose levels (Figure 3). Initial glucose levels greater than 200 mg/dL were associated with higher mortality only in nondiabetic patients (OR 2.1; 95% CI 1.4 to 3.0) but not in diabetic patients (OR 1.0; 95% CI 0.2 to 4.7), whereas glucose levels less than 100 mg/dL were associated with higher mortality mainly in the diabetic population (OR 2.3; 95% CI 1.6 to 3.3) and to a lesser extent in nondiabetic patients (OR 1.1; 95% CI 1.03 to 1.14).

LIMITATIONS

There are a number of limitations to our study. We prospectively enrolled patients according to suspicion of infection at the ED evaluation; thus, we did not integrate longitudinal information from the hospital course, and thus some patients ultimately found to have a noninfectious diagnosis may have falsely been included. Our analysis does not include more detailed information about type and duration of diabetes and weight of patients, which could

provide important further insights. Also, we did not assess how hyperglycemia was treated in patients with and without diabetes on admission and during the hospital stay. Finally, it remains unproven from this observational analysis whether the association of hyperglycemia and mortality in patients without diabetes mirrors the toxic effects of hyperglycemia or whether hyperglycemia is rather a marker of stress and severity. It is possible that unmeasured confounders are driving this association or that the hyperglycemia in nondiabetic patients or hypoglycemia in diabetic patients simply reflects the metabolic disturbances indicative of critically ill patients unable to maintain their baseline homeostatic state. To address this concern, we adjusted our analysis for sepsis syndrome and disease severity. Still, remaining unmeasured confounding cannot be excluded and may explain some of the effects.

DISCUSSION

Within this analysis incorporating data from 3 relatively large, distinct, prospectively collected cohorts of septic patients, a medical history of diabetes was not associated with increased inhospital mortality. In fact, there was a trend toward lower mortality of diabetic patients after adjustment for age, sex, severity, and sepsis syndrome.

Although previous studies investigated the association of diabetes and mortality predominantly in the later and most severe stages of sepsis in ICU patients with organ dysfunction and shock,^{24,25,28} our analysis includes a more broad spectrum of ED patients with suspected infection at an early sepsis stage. At this point, physicians have to make decisions about adequate allocation of health care resources and therapeutic options, which include decisions about outpatient and inhospital treatment, intensity of diagnostic evaluation, route of antimicrobial therapy, and evaluation for early discharge. Our observation that diabetes per se is not associated with a higher risk for mortality may have implications for initial triage decisions. Still, factors other than mortality, such as increased attentiveness to patients with diabetes or a lower threshold for admission, may affect these associations.

An interesting and notable finding of this study was the association between hyperglycemia and increased mortality in patients without diabetes, but not in patients with diabetes. A similar association was previously found in critically ill ICU patients with and without sepsis.²⁸ These findings suggest that relatively acute hyperglycemia of critical illness may have a different pathophysiologic effect in patients without diabetes compared with patients with preexisting diabetes. Conversely, in patients with low glucose levels, there was a significantly increased mortality in individuals with diabetes exclusively. These findings suggest that patients with diabetes tolerate hyperglycemic episodes much better compared with patients without diabetes and that patients with diabetes have a relative intolerance of hypoglycemic episodes. Although we did adjust for severity and sepsis syndrome, we cannot exclude that residual confounding explains some of these effects because glucose is a well-known stress parameter, which increases in response to endogenous catecholamines and cortisol production, particularly in patients without diabetes.

Although preclinical studies suggest that diabetes and especially hyperglycemia reduce polymorphonuclear neutrophil cell performance, influence cytokine regulation, and induce endothelial cell activation, resulting in an impaired host defense,⁷⁻¹⁰ it is unclear whether diabetes is indeed a risk factor for mortality for patients with septic diseases.¹² In general, patients with diabetes have been found to be more prone to acquire an infection,³⁵ but in terms of the influence on outcome, this is far less clear. Higher mortality rates in patients with diabetes were reported in some clinical trials,¹³⁻²⁰ whereas others found no influence^{1,21-24} or even protective effects of diabetes in sepsis.²⁵⁻²⁸ Different mechanisms

for these protective effects have been discussed, including anti-inflammatory effects of exogenously administered insulin, prevention of acute lung injury,²⁶ adaptation to previous oxidant stress,³⁶ and an improved nutritional or caloric substrate in obese patients with diabetes.³⁷ In a large epidemiologic study using US National Hospital Discharge Survey data of sepsis patients, patients with diabetes were less likely to develop acute respiratory failure (9% versus 14%; $P<.05$) and had a significantly lower mortality rate (18.5% versus 20.6%; $P<.05$).²⁵ Similarly, a study found that in patients with septic shock, diabetes was associated with lower risk for acute respiratory distress syndrome.²⁶ A protective effect of diabetes on mortality of critically ill patients was also suggested in a recent study including data from parallel retrospective and prospective ICU patient cohorts.²⁸ Finally, a population-based cohort study in Denmark with 598 community-acquired pneumococcal bacteremia patients found a trend toward lower 30- and 90-day mortality rates in patients with diabetes (adjusted mortality rate ratio 0.6; 95% CI 0.3 to 1.2).²⁷ In line with these studies, we found a trend toward lower mortality of diabetes when adjusted for different confounders and disease severity.

There are different possible explanations for an association of diabetes with lower mortality. Moss et al²⁶ speculated that a blunted inflammatory response, impaired neutrophil function, and altered neutrophil-endothelial interaction could protect patients with diabetes from development of secondary sepsis-related complications, such as acute respiratory distress syndrome. Similarly, a protective effect of obesity has been postulated, and clinical studies have found lower mortality in obese patients compared with severity-matched nonobese patients, with a linear correlation of body mass index and risk for mortality in the critical care setting.³⁷ A possible explanation for this finding is that obesity provides a nutritional reserve that, in times of stress and increased metabolic demand, helps to prevent the long-term complications associated with sepsis.³⁷ In addition, anti-inflammatory effects of insulin therapy have been postulated because previous studies have shown that insulin suppresses the production of a range of early proinflammatory substances, including tumor necrosis factor α , macrophage migration inhibitory factor, superoxide anions, and intranuclear nuclear factor- κ B.³⁸⁻⁴⁰ In addition, patients with diabetes may use other medications such as statins more frequently, which could have a protective effect that confounds the association.⁴¹ Finally, better diagnostic surveillance of patients with diabetes and higher rates of inpatient treatment in patients with diabetes may result in lower-than-expected mortality from sepsis.

In conclusion, we found no evidence for a harmful association of diabetes and mortality in patients with a suspected infection who were admitted to the hospital from the ED with different severities of sepsis. High initial glucose levels were associated with adverse outcome in the nondiabetic population but not in patients with diabetes. Further investigation is warranted to determine the mechanism for these effects.

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Figure 1.

Association of diabetes and mortality in multivariate logistic regression analysis. Multivariable models (cohort 1, 2 and 3) are adjusted for sepsis syndrome, sepsis severity, age, sex, and glucose range; the overall model refers to a hierarchic model adjusted for sepsis syndrome, sepsis severity, age, and sex, taking the different study sites into account.

Figure 2.

Mortality in patients with and without diabetes, stratified by initial glucose range (n=7,754). Differences in patients with diabetes and without diabetes are significant for glucose levels <100mg/dl ($p<0.01$) and 200mg/dl ($p<0.01$).

Figure 3.

Association of high glucose levels and low glucose levels with mortality in patients with and without diabetes. Results are derived from hierarchic models adjusted for sepsis syndrome, sepsis severity, age, and sex, with inclusion of an interaction term between diabetes and glucose levels.

Table

Patient characteristics.

Covariates	Cohort 1 (n=2,132)	Cohort 2 (n=4,618)	Cohort 3 (n=1,004)	Overall (n=7,754)
Demographics				
Age, y, mean (SD)	60 (20)	60 (20)	54 (19)	59 (20)
Male sex, No. (%)	1,020 (47.8)	2,236 (48.4)	526 (52.4)	3,782 (48.8)
Race, No. (%)				
White	1,610 (75.5)	3,372 (73.0)	467 (46.5)	5,449 (70.3)
Black	296 (13.9)	554 (12.0)	471 (46.9)	1,321 (17.0)
Asian	59 (2.8)	126 (2.7)	6 (0.6)	191 (2.5)
Other	167 (7.8)	566 (12.3)	50 (6.0)	783 (10.1)
Comorbidities, No. (%)				
Congestive heart failure	249 (11.7)	446 (9.7)	98 (9.8)	793 (10.2)
COPD	268 (12.6)	357 (7.7)	159 (15.8)	784 (10.1)
Diabetes	565 (26.5)	1,040 (22.5)	239 (23.8)	1,844 (23.7)
Malignancy	253 (11.9)	689 (14.9)	64 (6.4)	1,006 (12.9)
Renal disease	266 (12.5)	414 (9.0)	66 (6.6)	746 (9.62)
Laboratory analysis on admission, mean (SD)				
WBC count ($10^9/L$)	11.7 (8.1)	11.7 (11.2)	11.8 (8.0)	11.7 (7.9)
Platelets ($1,000/\mu L$)	265 (128)	268 (129)	255 (142)	265 (131)
Glucose levels, mg/dL	139 (81)	136 (73)	144 (110)	138 (81)
Sepsis category, No. (%)				
Sepsis	1,015 (47.6)	2,953 (64)	492 (49)	4,460 (57.5)
Severe sepsis	996 (46.7)	1,491 (32.3)	381 (38)	2,868 (37)
Septic shock	121 (5.7)	174 (3.8)	131 (13.1)	426 (5.5)
Outcomes				
Length of stay, days, mean (SD)	5.5 (7)	5.4 (7.1)	5.8 (7.2)	5.5 (7.1)
ICU admission, No. (%)	299 (14.0)	800 (17.3)	213 (21.2)	1,312 (16.9)
Mortality, No. (%)	83 (3.9)	193 (4.2)	61 (6.1)	337 (4.3)

COPD, Chronic obstructive pulmonary disease.