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Hyperglycemia: An Independent Marker of In-Hospital Mortality in Patients with Undiagnosed Diabetes

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Admission hyperglycemia has been associated with increased hospital mortality in critically ill patients; however, it is not known whether hyperglycemia in patients admitted to general hospital wards is associated with poor outcome. The aim of this study was to determine the prevalence of in-hospital hyperglycemia and determine the survival and functional outcome of patients with hyperglycemia with and without a history of diabetes. We reviewed the medical records of 2030 consecutive adult patients admitted to Georgia Baptist Medical Center, a community teaching hospital in downtown Atlanta, GA, from July 1, 1998, to October 20, 1998. New hyperglycemia was defined as an admission or in-hospital fasting glucose level of 126 mg/dl (7 mmol/liter) or more or a random blood glucose level of 200 mg/dl (11.1 mmol/liter) or more on 2 or more determinations. Hyperglycemia was present in 38% of patients admitted to the hospital, of whom 26% had a known history of diabetes, and 12% had no history of diabetes before the admission. Newly discovered hyperglycemia was associated with higher in-hospital mortality rate (16%) compared with those patients with a prior history of diabetes (3%) and subjects with normoglycemia (1.7%; both *P* < 0.01). In addition, new hyperglycemic patients had a longer length of hospital stay, a higher admission rate to an intensive care unit, and were less likely to be discharged to home, frequently requiring transfer to a transitional care unit or nursing home facility.

Our results indicate that in-hospital hyperglycemia is a common finding and represents an important marker of poor clinical outcome and mortality in patients with and without a history of diabetes. Patients with newly diagnosed hyperglycemia had a significantly higher mortality rate and a lower functional outcome than patients with a known history of diabetes or normoglycemia. (*J Clin Endocrinol Metab* 87: 978–982, 2002)

A RELATIONSHIP between admission plasma glucose concentration and in-hospital mortality in patients with acute myocardial infarction and acute stroke has been established (1–6). An increased risk of congestive heart failure and increased mortality rate are seen both during the acute phase and long-term follow-up of diabetic patients with myocardial infarction (4, 7). Similarly, several studies have indicated that patients with diabetes are more likely to die or to have substantial neurological disability after acute stroke than nondiabetic subjects (6, 8–13). There is dispute, however, about whether a raised blood glucose concentration is independently associated with a poor prognosis (11, 14, 15) or may indicate a more severe illness with an increased response to stress (8, 13, 16–18). Furthermore, it is not known whether hyperglycemia in patients without critical illness admitted to general hospital wards is associated with poor outcome. If stress hyperglycemia is proven to be an independent predictor of poor outcome, a policy for early detection and glucose control may be warranted.

The aim of this study was to determine the prevalence of diabetes and hyperglycemia in hospitalized patients at a community hospital and to determine the effects of newly diagnosed hyperglycemia on survival and functional outcome after adjusting for known prognostic factors.

Abbreviation: ICU, Intensive care unit.

Materials and Methods

The medical records of 2030 consecutive adult patients admitted to Georgia Baptist Medical Center, a community teaching hospital in downtown Atlanta, GA, from July 1, 1998, to October 20, 1998, were reviewed. Of the 2030 admitted patients, 144 patients (7%) were excluded because no blood glucose measurement was recorded during the hospital stay. The remaining patients who had 1 or more glucose measurements made were divided into 3 study groups. A normoglycemic group included those patients with normal plasma glucose and no previous history of diabetes. Patients with hyperglycemia were subdivided between those with a previous history of diabetes (known diabetics) and those without a previous history of diabetes (new hyperglycemia). Hyperglycemia was defined as an admission or in-hospital fasting blood glucose level of 126 mg/dl (7 mmol/liter) or more or a random blood glucose level of 200 mg/dl (11.1 mmol/liter) or more on 2 or more determinations. Fasting blood glucose were those samples drawn from patients kept NPO or samples drawn between 0400–0600 h. Information regarding types of iv fluid was not recorded in this study; thus, it is possible that some patients may have received dextrose solutions at the time of hyperglycemia. Patient information was collected regarding demographic characteristics, blood glucose levels on admission and during hospital stay, concurrent medical diagnoses, medical treatment, and hospital outcome, including mortality and disposition at discharge.

The primary end point of the study was in-hospital mortality. Secondary end points included treatment of hyperglycemia, length of hospital stay, and patient disposition at discharge (discharge to personal home, transitional care or rehabilitation unit, and nursing home facility). In addition to blood glucose levels, prognostic variables considered were age, gender, body mass index, admission blood pressure, smoking status, coronary heart disease or renal failure, presence of infection, and the need for intensive care unit (ICU) admission.

Statistical analysis

To compare baseline demographics and clinical characteristics between groups, ANOVA with Scheffé's method was used for continuous variables, with log transformations when necessary. For categorical variables, χ^2 analysis was used, with a Bonferonni correction when applicable. Multiple logistic regression and adjusted odds ratios were employed to determine the influence of demographic and clinical characteristics on mortality rates and length of stay. $P < 0.05$ was considered significant. StatView version 5.0 (SAS Institute, Inc., Cary, NC) was the statistical software used for the analysis.

Results

Of the 1886 study patients, 1168 (62%) had 1 or more blood glucose measurements within normal limits. The known diabetes group consisted of 495 patients (26%) with a history of diabetes mellitus documented before admission. The newly diagnosed hyperglycemia group consisted of 223 (12%) patients with no prior history of diabetes who were found to have an admission or in-hospital fasting glucose level greater than 126 mg/dl (7 mmol/liter) or a random blood glucose level greater than 200 mg/dl (11.1 mmol/liter) on 2 or more determinations.

The clinical characteristics of the three study groups are shown in Table 1. There were no differences in the mean age, gender distribution, racial distribution, or admission blood pressure among the three groups. Patients with known diabetes tended to have a higher age and body mass index; however, these differences were not statistically significant. As expected, patients with known diabetes had significantly higher fasting and random blood glucose levels compared with the normoglycemia group ($P < 0.01$). The admission blood glucose level in patients with known diabetes (12.8 ± 1 mmol/liter) was higher than that in the new hyperglycemia group (10.5 ± 1 mmol/liter), but results were not statistically significant. We observed no differences among the three groups in the proportion of patients who were admitted to a medicine service *vs.* a surgical service.

Patients with new hyperglycemia were more likely to be admitted to the ICU (29%) and had a longer length of hospital stay (9.7 ± 0.7 d) compared with patients with a prior diagnosis of diabetes (14% and 5.5 ± 0.2 d; both $P < 0.01$) and normoglycemic subjects (9% and 4.5 ± 0.1 d; both, $P < 0.01$). In addition, new hyperglycemic patients were less likely to be discharged home and were more likely to be discharged to a transitional or extended care facility compared with known diabetic and normoglycemic patients (Table 2).

Patients with new hyperglycemia had a higher in-hospital mortality (16%) compared with patients with a known history of diabetes (3%) and normoglycemia (1.7%; both $P < 0.01$) (Fig. 1). The increased mortality was observed both in patients admitted to the ICU and in patients admitted to a general medicine or surgery wards (Table 3). The mortality

TABLE 1. Patient characteristics on admission

	New hyperglycemia	Known diabetes	Normoglycemia
No. of patients (%)	223 (12)	495 (26)	1168 (62)
Mean age (yr)	59 ± 1	63 ± 1	54 ± 1
Gender (M/F)	44/56	39/61	42/58
Body mass index (kg/m^2)	26 ± 0.6	29 ± 0.5	26 ± 0.2
Race			
Caucasian (%)	46	37	48
Black (%)	52	62	51
Mean BP (mm Hg)	97 ± 2	101 ± 1	97 ± 1
Blood glucose (mmol/liter)	10.5 ± 1[a]	12.8 ± 1[a]	6 ± 0.06
Admission service			
Medicine (%)	55	65	52
Surgery (%)	37	24	33
ICU admissions (%)	29[a,b]	14[a]	9

Results are ±SEM.
[a] $P < 0.01$ *vs.* normoglycemia.
[b] $P < 0.001$ *vs.* known diabetes.

TABLE 2. Length of stay, mortality, and disposition at discharge

	New hyperglycemia	Known diabetes	Normoglycemia
Length of stay (d)	9 ± 0.7[a,b]	5.5 ± 0.2	4.5 ± 0.1
Mortality (%)	16[a,b]	3	1.7
Disposition at discharge			
Home (%)	56[a,b]	74[a]	84
TCU (%)	20[a]	15[c]	10
Nursing home (%)	8[d]	9[c]	4

Results are ±SEM. TCU, Transitional care unit.
[a] $P < 0.001$ *vs.* normoglycemia.
[b] $P < 0.001$ *vs.* known diabetes.
[c] $P < 0.01$ *vs.* normoglycemia.
[d] $P < 0.02$ *vs.* normoglycemia.

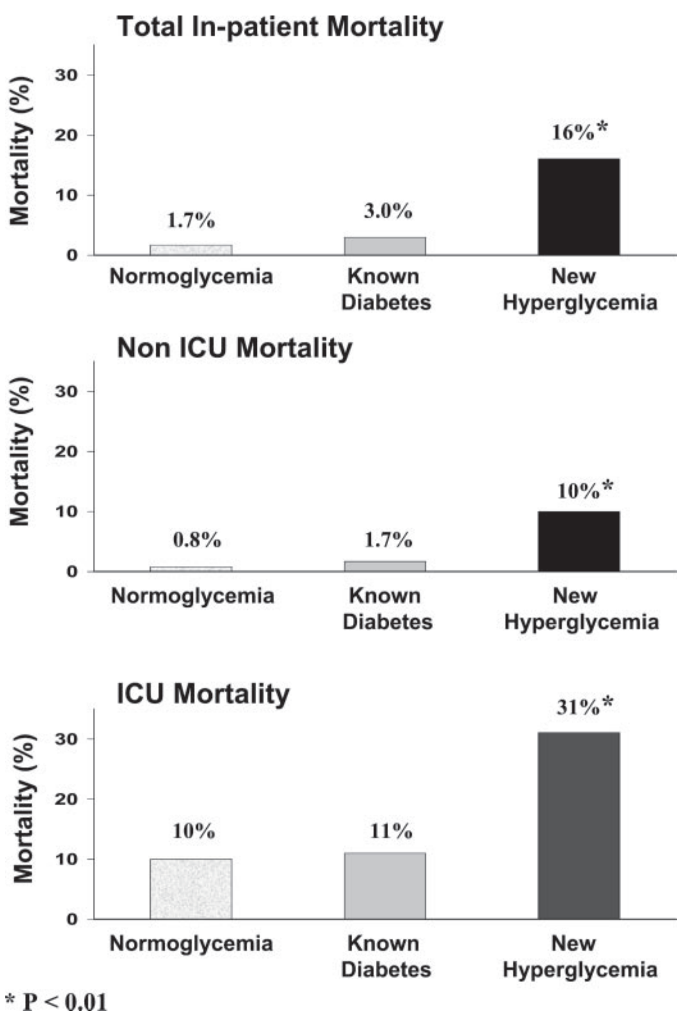

FIG. 1. In-hospital mortality n patients with normoglycimia, known diabetes, and newly discovered hyperglycemia.

TABLE 3. ICU and non-ICU mortality

	New hyperglycemia	Known diabetes	Normo-glycemia
Total no. of patients (%)	223 (12)	495 (26)	1168 (62)
Total mortality (%)	36 (16)[a]	15 (3.0)	20 (1.7)
Total non-ICU admissions (%)	159 (10)	421 (26)	1063 (64)
Non-ICU mortality (%)	16 (10)[a]	7 (1.7)	9 (0.8)
Total ICU admission (%)	65 (27)	71 (29)	107 (44)
ICU mortality (%)	20 (31)[a]	8 (11)	11 (10)

[a] $P < 0.001$.

TABLE 4. Clinical characteristics of deceased patients

	New hyperglycemia	Known diabetes	Normo-glycemia
No. of patients	36	15	20
Mean age (yr)	59 ± 4	66 ± 6[a]	74 ± 3[b]
Gender (M/F)	17/19	7/8	12/8
L.O.S. (d)	7.6 ± 2	4.3 ± 1	7 ± 2
ICU admission (%)	20 (56)	8 (54)	11 (55)
Admission BG (mmol/liter)	10.1 ± 1	13 ± 2[b]	6.6 ± 0.5[b]
Mean FBG (mmol/liter)	9.7 ± 0.4	9.7 ± 1.4	5.2 ± 0.4[b]
Mean RBG (mmol/liter)	10.6 ± 0.6	14.3 ± 1.8[b]	6.3 ± 0.4[b]
Cause of death			
Infection (%)	12 (33)	4 (27)	4 (20)
Cardiovascular (%)	10 (28)	8 (53)	10 (50)
Neurologic events (%)	7 (19)	2 (13)	2 (10)
Malignancy (%)	3 (8)	1 (7)	1 (5)
Other (%)	6 (17)	3 (20)	3 (15)

Values are ± SEM. L.O.S., length of stay; BG, blood glucose; FBG, fasting blood glucose; RBG, random blood glucose.
[a] $P < 0.05$ *vs.* new hyperglycemia.
[b] $P < 0.01$ *vs.* new hyperglycemia.

rate in non-ICU patients was 0.8% in patients with normoglycemia, 1.7% in those with previous history of diabetes, and 10% in patients with new hyperglycemia (both $P < 0.01$). Among patients admitted to the ICU, patients with newly diagnosed hyperglycemia had a 3-fold higher mortality rate (31%) than patients with a known history of diabetes or with normoglycemia who had ICU mortalities of 10% and 11.3%, respectively ($P < 0.01$). Although the mortality rate in known diabetics was higher than that in the normoglycemic group, the differences did not reach statistical significance.

The clinical characteristics of deceased patients are shown in Table 4. The mean age of patients with newly discovered hyperglycemia who died was 59 ± 4 yr (±SEM). These patients were significantly younger than known diabetics (66 ± 6 yr) or normoglycemic patients (74 ± 3 yr). Among the deceased patients, we observed no significant differences in gender, length of hospital stay, or percentage of patients admitted to the ICU among the three study groups. The mean admission and random blood glucose levels in new hyperglycemic patients who subsequently died were lower than those in patients who died in the diabetic group; however, there were no statistically significant differences in admission, fasting, or random mean blood glucose levels between the two hyperglycemic groups. New hyperglycemia patients had a higher mortality rate due to infectious disorders and acute neurological events than the other two groups, and were less likely to die of cardiovascular causes compared with normoglycemic patients and known diabetic subjects. As some patients had one or more ongoing medical problems, the total cause of death percentages in Table 3 may add up to more than 100%.

Multivariate odds ratios for mortality were calculated using logistic regression and compared with those of the normoglycemia group. Odds ratios were adjusted for age, body mass index, gender, hypertension, coronary artery disease, presence of infection, renal failure, and ICU admission. Even after adjustment for these variables, the new hyperglycemia group had an 18.3-fold increased mortality rate compared with a 2.7-fold increase in the known diabetes group.

Newly diagnosed hyperglycemia was frequently left untreated. During the hospital course, only 13% had orders for a diabetic diet, 2% were prescribed oral hypoglycemic agents, 6% received scheduled dose insulin, and 35% received sliding scale insulin. These treatment modalities were significantly lower than those in patients with a history of diabetes, in whom 53% had orders for a diabetic diet, 33% were prescribed oral hypoglycemic agents, 32% received scheduled dose insulin, and 77% received insulin therapy.

Discussion

We found that hyperglycemia was present in 38% of patients admitted to the hospital, and that one third of these patients had no history of diabetes before the admission. Patients with new hyperglycemia had significantly higher in-hospital mortality rate and worse functional outcome than patients with a prior history of diabetes and subjects with normoglycemia. In addition, patients with new hyperglycemia had an increased length of hospital stay, were more likely to require admission to an ICU, and were more likely to require transfer to a transitional care unit or nursing home facility at discharge.

Admission hyperglycemia has been associated with increased morbidity and mortality in patients with acute critical illnesses, such as myocardial infarction and stroke (1–12). In patients with acute myocardial infarction, hyperglycemia has been associated with increased risk of mortality, congestive heart failure, and cardiogenic shock in patients with and without diabetes (1, 3, 6, 20–22). Similarly, hyperglycemia in the acute phase of stroke has been suggested as a predictor of worse prognosis, in terms of both mortality and residual disability (6, 17, 18, 19, 23, 24). This study confirms these observations, but in addition it indicates that hyperglycemia is an important marker of poor clinical outcome and mortality not only in critical patients admitted to the ICU, but also in patients admitted to general medicine and surgery wards. Using multivariate odds ratios for mortality adjusted for age, body mass index, gender, hypertension, coronary artery disease, presence of infection, renal failure, and ICU admission, we found that patients with new hyperglycemia had an 18.3-fold increase in mortality rate compared with a 2.7-fold increase in the known diabetes group.

A number of features suggests that patients with newly diagnosed hyperglycemia were more severely ill than patients with known diabetes or without hyperglycemia. Patients with newly diagnosed hyperglycemia were more likely to be admitted to the ICU, had a longer length of hospital stay, and were less likely to be discharged home. More strikingly, 16% died compared with 3% of patients with a known history of diabetes and 1.7% of the normoglycemic group. An additional finding that suggests that new hyperglycemia represents a marker of a more severe illness and is not the primary cause of the increased morbidity and mortality is that the admission and random blood glucose concentrations in patients with new hyperglycemia were lower than those in patients with known diabetes. Stress hyperglycemia, defined as a transient increase in blood glucose concentration during acute physiological illness, represents two distinct populations: those with undiagnosed diabetes or impaired glucose tolerance, and those who develop hyperglycemia as the result of the severe stress and increased counterregulatory hormones. Although the underlying mechanisms for the development of stress hyperglycemia are not fully understood, several potential mechanisms have been proposed. These include increased substrate availability in the form of lactate (16, 25, 26), increased gluconeogenesis and decreased glycogenolysis due to increased secretion of counterregulatory hormones (catecholamines, cortisol, and glucagon) (12, 27, 28), and peripheral insulin resistance (29, 30). Although in such patients, the high morbidity and mortality relate to the associated illness precipitating the stress, hyperglycemia itself may contribute to morbidity by creating a toxic cellular milieu (31–33), causing intracellular and extracellular dehydration (34), inducing electrolyte abnormalities, and depressing immune function (35).

Our study did not address the question of whether treatment of hyperglycemia may reduce the high morbidity and mortality associated with hyperglycemia in patients with and without a history of diabetes. Recently, Van den Berghe *et al.* (36) reported that among mechanical ventilated adult patients admitted to an ICU, strict normalization of blood glucose levels (4.5–6.1 mmol/liter) with continuous infusion of insulin compared with a restrictive insulin regimen to maintain blood glucose levels between 10–12 mmol/liter resulted in reduced hospital morbidity and mortality. The intensive insulin schedule significantly reduced ICU mortality by 43% (death odds ratio, 0.52; range, 0.33–0.81), hospital mortality by 34%, mean ICU stay by 22%, and incidence of bacteremia and hemodialysis by 50%. These results suggest that strict glucose control in hospitalized patients with hyperglycemia is warranted.

One limitation of our study is that we were not able to determine the percentage of patients with latent or unrecognized diabetes because of the lack of hemoglobin A_{1C} testing and the lack of follow-up after discharge. In agreement with a previous report (37), we found that 12% or one third of all hyperglycemic patients on both medical and surgical services had no prior history of diabetes. We believe that newly diagnosed hyperglycemia is usually considered a transient finding in response to the acute illness not requiring medical intervention, as indicated by the fact that more than two thirds of these patients did not receive diabetic diet or antidiabetic drug therapy. However, given the average delay of a decade between the onset and the diagnosis of diabetes (37, 38), further evaluation of new hyperglycemic patients with in-patient determination of hemoglobin A_{1C} may allow earlier diagnosis and treatment, which may prevent the development of chronic complications of diabetes.

In conclusion, we have shown that in-hospital hyperglycemia is a common finding and should be considered an important marker of poor clinical outcome and increased mortality, in particular in patients without a history of diabetes. Patients with new hyperglycemia admitted to critical care areas or to general medical and surgical wards had a significantly higher mortality rate and lower functional outcome than patients with a known history of diabetes or normoglycemia. Our observations indicate that all hospitalized patients should be screened for hyperglycemia.

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