

## Original Article

# Glycated hemoglobin A1C and diabetes mellitus in critically ill patients

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**BACKGROUND:** Hyperglycemia has been detected in many critically ill patients in the department of emergency medicine. But its mechanism and prognosis have not been well elucidated. In this study, we measured the serum level of glycated hemoglobin A1C (HbA1c) in critically ill patients to evaluate the effects of hyperglycemia on the prognosis of the patients.

**METHODS:** A total of 826 critically ill patients, who had been treated at the Department of Emergency Medicine of Chaoyang Hospital during October 2006 and November 2007, were divided into a diabetes mellitus group ( $n=184$ ) and a non-diabetes mellitus group (642) according to whether they had diabetes mellitus. Fasting glucose and HbA1c were measured in all patients. Those in the diabetes mellitus group were further assigned to a drug therapy subgroup and a non-drug therapy subgroup; the serum level of HbA1c and its relationship with short-term outcome were evaluated.

**RESULTS:** Fasting glucose increased in 78.8% of the patients (88.6% in the diabetes mellitus group, and 75.9% in the non-diabetes mellitus group,  $P<0.05$ ), and HbA1c was elevated in 45.5% of the patients (78.3% in the diabetes mellitus group, and 36.1% in the non-diabetes mellitus group,  $P<0.01$ ). Fasting glucose, HbA1c and 28-day mortality were improved more significantly ( $P<0.01$ ) in the drug therapy subgroup than in the non-drug therapy subgroup. The 28-day mortality was more significantly different in patients with fasting blood glucose  $>8.33$  mmol/L than in those with fasting blood glucose  $<8.33$  mmol/L.

**CONCLUSIONS:** Hyperglycemia of critically ill patients could not totally attribute to stress response, especially in those who have no history of diabetes mellitus. Prognosis of hyperglycemia may vary among critically ill patients.

**KEY WORDS:** Glycosylated hemoglobin A1C; Diabetes mellitus; Hyperglycemia; Prognosis; Critically ill patients

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## INTRODUCTION

Hyperglycemia has been detected in many critically ill patients in the department of emergency medicine.<sup>[1]</sup> Some of these patients have a history of diabetes mellitus and have been controlled with anti-hyperglycemia agents or insulin, whereas some are not although they have been confirmed to have diabetes after further examinations. To the present, the mechanism and prognosis of hyperglycemia in critically ill patients have not been well elucidated. In this study,

we tested the serum level of glycated hemoglobin A1C (HbA1c) in critically ill patients to identify the effects of hyperglycemia on the prognosis of the patients.

## METHODS

### Patients

A total of 826 critically ill patients, 436 males and 390 females, aged 18 to 96 years (mean age  $68\pm 13$  years old), were enrolled in this study. They were treated

for diabetic ketoacidosis (5 patients), pericarditis (2 patients), encephalitis (3 patients), severe pneumonia or infection (183 patients), acute heart failure (92 patients), acute coronary syndrome (193 patients), severe cardiac arrhythmia (36 patients), heart arrest (12 patients), acute episode of chronic bronchitis (161 patients), pulmonary embolism (24 patients), severe asthma (14 patients), or acute cerebrovascular disease (101 patients) at the Department of Emergency Medicine of Beijing Chaoyang Hospital during the period of October 2006 and November 2007. Exclusion criteria were: 1) age younger than 18 years; 2) pregnant women; 3) confirmed malignant tumors; 4) uremia; 5) living for less than 24 hours after cardiopulmonary resuscitation; 6) anemia or other hematologic diseases; 7) hyperthyroidism; 8) alimentary tract hemorrhage; and 9) physical and chemical injuries and intoxication.

## Methods

Personal information including age, gender, and medical history was collected from all the patients. Fasting blood glucose (glucose-6-phosphate dehydrogenase method; Accu-Check blood glucose analyzer, USA) and HbA1c (HPLC method; HLC-723G7 automatic glycosylated hemoglobin analyzer, Japan) were determined within 1 hour after emergency admission. APACHE II and EWS were used to identify hyperglycemia.

## Statistical analysis

SPSS 12.0 statistical software package was used for data analysis. The data were expressed as mean  $\pm$  standard deviation. The Chi-square test was used for comparison of positive rate and mortality, and analysis of variance (ANOVA) was used for analysis of quantitative data. A *P* value of less than 0.05 was considered statistically significant.

## RESULTS

No significant difference was found in age, gender and APACHE II scores among the drug therapy subgroup, non-drug therapy subgroup, and non-diabetes mellitus group. However, 28-day mortality was significantly different in the three groups.

Of 651 patients with hyperglycemia, 275 (151 males, 124 females, average age  $66 \pm 16$  years) had normal HbA1c, and 376 (203 males, 173 females, average age  $70 \pm 17$  years old) had elevated HbA1c ( $P > 0.05$ ). Newly diagnosed diabetes and the 28-day mortality of these

**Table 1.** The 28-day mortality and diabetes diagnosis of the 651 patients with hyperglycemia

Groups	<i>n</i>	Newly diagnosed diabetes	Deaths	Mortality
Normal HbA1c	275	23	16	8.70
Elevated HbA1c	376	362	46	12.15

patients are shown in Table 1.

Three hundred and eighty-five of the 651 hyperglycemia patients were confirmed to be diabetics, although 155 participants didn't have a history of diabetes. A total of 266 patients with stress-induced hyperglycemia were found in the non-diabetes mellitus group.

The 28-day mortality of the elevated HbA1c group (12.23%) was significantly higher than that of the normal HbA1c group (5.82%) ( $P = 0.001$ ). In the elevated HbA1c group, the 28-day mortality of the patients without a history of diabetes (29/151, 19.21%) was significantly higher than that of the patients with definite diabetes (15/211, 7.11%) ( $P = 0.000$ ).

## DISCUSSION

In the acute phase of stress response of critically ill patients, the nervous-endocrine system faces stress disturbance, and inflammatory mediators are excessively released under intensive stimulation of multiple kinds of disease factors. This can lead to abnormalities in energy and substance metabolism in organisms, and glycometabolism disorder characterized by hyperglycemia is frequently seen.<sup>[2-4]</sup> Abnormal hyperglycemia can lead to increases in various cytokines, and is one of the disadvantageous factors of functional defect in multiple organs.<sup>[5,6]</sup> Stress induced hyperglycemia is commonly seen in critically ill patients, and some of the critically ill patients with abnormally elevated blood glucose (including those with or without definite medical history of diabetes) fail to control the blood glucose. Some of them suffer from stress hyperglycemia, a few show hyperglycemia due to other reasons such as intravenous infusion of glucose. It is commonly proposed that the patient can be diagnosed with stress hyperglycemia when randomly measured blood glucose is not lower than 11.1 mmol/L. We found in the present study that 78.81% of the the 826 patients had hyperglycemia, but not all could be diagnosed as having stress induced hyperglycemia. We propose that the incidence of stress-induced hyperglycemia cannot be truly assessed even a judgment is made

whether the patient has a history of diabetes because a considerable number of the critically ill patients didn't know they were diabetics. A total of 155 patients who denied a history of diabetes were finally confirmed to have diabetes, accounting for 23.81% of the patients with hyperglycemia (155/651). After excluding the hyperglycemia induced by failure in blood glucose control in the diabetics, 266 patients were diagnosed with stress induced hyperglycemia. Therefore, our results indicate that abnormal hyperglycemia in critically ill patients can not be easily explained as blood glucose elevation induced by stress response.

HbA1c level is correlated with blood glucose level and can represent the average blood glucose level within 4 to 12 weeks and make up for the shortage that conventional blood glucose determination can only represent transient blood glucose.<sup>[7]</sup> HbA1c monitoring can be used to judge the reason for hyperglycemia as an adjunctive parameter. Investigations<sup>[8,9]</sup> have shown that HbA1c is a parameter for identifying stress hyperglycemia and diabetic hyperglycemia. Our results indicate that 376 patients had elevated HbA1c and 362 patients were found to have diabetes; 275 patients had normal HbA1c and 252 patients were diagnosed as non-diabetics. Among the 155 patients, 151 who denied a medical history of diabetes but finally diagnosed with diabetes showed increased HbA1c. Therefore, HbA1c monitoring should be used for critically ill patients with abnormal hyperglycemia; if the results indicated abnormal elevation, diabetes should be suspected in the patients who had no history of diabetes.<sup>[10]</sup>

The 28-day follow-up of the 651 patients found that the mortality in the elevated HbA1c group (12.23%) was significantly higher than that in the normal HbA1c group (5.82%) ( $P=0.001$ ). It is easy to understand that the abnormal elevation in HbA1c indicates that the control of blood glucose may be not satisfactory, but studies have confirmed that abnormal elevation in blood glucose is an independent risk factor for the poor prognosis of critically ill patients,<sup>[11-13]</sup> and strict control of blood glucose is one of the target treatments for these patients.<sup>[14-16]</sup> Our results also indicated that the 28-day mortality of the patients without a medical history of diabetes (29/151, 19.21%) was significantly higher than that of the patients with definite diabetes (15/211, 7.11%) ( $P=0.000$ ). Blood glucose control and complications of diabetes were not as satisfactory as those in patients without diabetes, but the prognosis of critical diseases was relatively satisfactory. The patients with clinically "recessive diabetes" had no adequate understanding of diabetes and

thus they could not come to hospitals for help in time, and their blood glucose level is abnormal for a long time with occurrence of serious diabetic complications. The complications of the elevated blood glucose become serious, and the possibility of infections increases and the risks for cerebrovascular diseases increases.<sup>[17-20]</sup> These factors can lead to serious conditions and poor prognosis of critically ill patients.

In general, hyperglycemia is frequently seen in critically ill patients. But those without a history of diabetes mellitus should be subjected to HbA1c detection so as to determine whether they suffer from hyperglycemia. Correct diagnosis and timely treatment of hyperglycemia are necessary to improve the survival rate of critically ill patients with elevated HbA1c.

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**Conflicts of interest:** The authors declare that there is no conflict of interest.

**Contributors:** Zhang HY designed the research, analyzed the data, and wrote the paper. All authors read and approved the final version.

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