A U-Shape Relationship between HbA1c and All-Cause Mortality Rate in Diabetic Patients Admitted for Severe Hypoglycemia: A 15-Year, Multicenter, Retrospective Survey

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Abstract: *Aims*: To evaluate the association between HbA1c and mortality rate, and the cause of death during admission in diabetic patients admitted for severe hypoglycemia.

Materials and Methods: From August 1998 to July 2013, we collected data from diabetic patients admitted with severe hypoglycemia at 12 middle and south China Medical Centers. The data collected includes demographic information and biochemical variables. Patients were divided into four groups according to HbA1c level: <6.0%, 6.0-6.9%, 7.0-7.9% and ≥8.0%.

Results: A total of 1522 diabetic patients were admitted for severe hypoglycemia during the study period, and 1117 underwent HbA1c testing. When HbA1c was<6.0%, 6.0-6.9%, 7.0-7.9% and ≥8.0%, the mortality rate was 7.1%, 2.8%, 3.7% and 6.8%, respectively. A significant difference was found between HbA1c<6.0% compared with HbA1c 6.0-6.9% (χ^2 =7.319, P=0.007), and between HbA1c 6.0-6.9% and HbA1c≥8.0% (χ^2=4.805, P=0.028). In total, 57 patients died. The causes of death included infection (n=33), stroke (n=7), cardiovascular disease complicated by heart failure (n=7), diabetic nephropathy complicated by renal failure (n=6), lung cancer (n=2), a stress ulcer complicated by hemorrhage (n=1) and cirrhosis complicated by hemorrhage (n=1).

Conclusions: There is a U-shape relationship between HbA1c and mortality rate during admission in diabetic patients admitted for severe hypoglycemia. Severe hypoglycemia may predict an increased risk of death in patients with lower and higher HbA1c.

Keywords: Severe hypoglycemia, HbA1c, Mortality rate.

INTRODUCTION

Both Diabetes Control and Complications Trial (DCCT) and UK Prospective Diabetes Study (UKPDS) indicate that intensive glucose control therapy should be aimed at decreasing HbA1c below 7.0% to reduce microvascular complications [1, 2]. However, hypoglycemia has been identified as the limiting factor that prevents diabetic patients from achieving good glycemic control [3]. Hypoglycemia can cause death in type 1 diabetes [4]. Recently, the ACCORD study was

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conducted in patients with type 2 diabetes, and this study found that severe hypoglycemia was a significant risk factor for death [5]. The mortality rates in participants who experienced at least one severe hypoglycemic event requiring any assistance (HA) were higher than in participants with no history of HA (6.9% *vs*. 4.1%) [6]. The NICE-SUGAR study that enrolled critically ill patients also showed that intensive glucose control leads to moderate and severe hypoglycemia, both of which are associated with an increased risk of death [7].

Our previous survey showed that diabetic patients with severe hypoglycemia had an all-cause mortality rate of 5%. We also found that the patients who died showed a trend toward a lower or higher HbA1c level [8]. Thus, we speculated that there is a U shape relationship between HbA1c and death in these patients. The previous survey had a limited sample size that was not sufficiently powered to draw a statistical conclusion. In this study, we enrolled more patients and tested our hypothesis of a U shape relationship between HbA1c and death in diabetic patients with severe hypoglycemia.

MATERIALS AND METHODS

Data Collection

From August 1998 to July 2013, we collected data from diabetic patients with severe hypoglycemia at 12 middle and south China Medical Centers. Each of the centers has more than 1 000 beds and serves 100-150 thousand people over the study period. Samples from patients with hypoglycemia over this 15-year period were identified using the ICD-9-CM coding system (250.8, 251.0, 251.1, and 251.2). The diagnosis of diabetes confirmed by both diabetes history and prescription claims for diabetes medications. Severe hypoglycemia was defined as a blood glucose level of <2.8 mmol/L and the requirement for the patient to be admitted to hospital or taken to the emergency department. If a patient had several episodes of severe hypoglycemia we analyzed him (her) as several patients. All patients were taking oral hypoglycemic agents, so the hypoglycemic episodes probably related to the treatment. In this analysis, all deaths were defined as death during admission. The data collected included demographic information and biochemical variables. The HbA1c level was assessed using high-pressure liquid chromatography (nine medical centers), affinity chromatography (two medical centers), or turbidimetric immunoinhibition assay (one medical center). Reference HbA1c values ranged from 4.5% to 6.5% at every center. The Chinese Ministry of Health provided the same quality control material during the same period to all medical centers. We divided all the patients into four groups according to HbA1c level: <6.0%, 6.0-6.9%, 7.0-7.9% and ≥8.0%.

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethical board of each participating hospital. All patients had provided written informed consent upon admission.

Statistical Methods

All statistical analyses were conducted using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was defined as $P<0.05$. The difference in the mortality rate between the four groups was compared using the Pearson Chi-square test.

Table 1: General Patient Characteristics

	<6.0%	6.0-6.9%	7.0-7.9%	≥8.0%
n	394	359	187	177
DM (type1/2)	13/381	11/348	9/178	7/170
Sex (M/F)	190/204	174/185	91/96	82/95
Age$^{\Delta}$ (yr)	72.4±10.9	72.7±10.0	74.8±9.5	70.0±12.5
AST* (mmol/L)	23 (9-852)	23 (10-695)	23 (9-108)	22 (8-177)
ALT* (mmol/L)	16 (58-1272)	16 (2-559)	17 (3-93)	22 (5-323)
Creatine*(mmol/L)	92 (9-1517)	95 (24-974)	108 (43-543)	94(43-1317)
UA* (μmol/L)	290(115-947)	311(137-1078)	306(79-640)	276(18-653)
TC$^{\Delta}$ (mmol/L)	4.2±1.2	4.2±1.1	4.2±1.2	4.1±1.1
TG* (mmol/L)	1.0 (0.2-18)	1.0 (0.3-4.7)	0.8 (0.2-5.9)	0.9 (0.2-4.7)

$^{\Delta}$mean ± standard deviation (SD); *median (range); DM: Diabetes mellitus; AST: Aspartate aminotransferase; ALT: Alanine transaminase; UA: Uric acid; TC: Total cholesterol; TG: Triglyceride.

RESULTS

General Characteristics

A total of 1522 diabetic patients were admitted for severe hypoglycemia during the study period. Of the 1522 patients, 1117 received the HbA1c test. The general characteristics and related biochemical variables of the patients are shown in Table **1**.

Comparison of Mortality Rate between Different HbA1c Level Groups

In HbA1c<6.0%, 6.0-6.9%, 7.0-7.9% and ≥8.0% groups, mortality rate was 7.1% (28/394), 2.8% (10/359), 3.7% (7/187) and 6.8% (12/177), respectively. A statistically significant difference was found between HbA1c<6.0% compared with HbA1c 6.0-6.9% (χ^2 =7.319, P=0.007). A statistically significant difference was also found between HbA1c 6.0-6.9% and HbA1c≥8.0% (χ^2=4.805, P=0.028; Figure **1**).

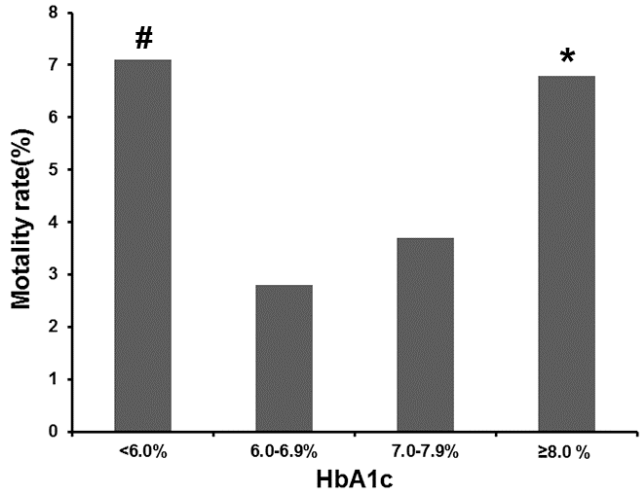

Figure 1: The association between HbA1c and mortality rate in diabetic patients admitted for severe hypoglycemia. In HbA1c<6.0%, 6.0-6.9%, 7.0-7.9% and ≥8.0% groups, mortality rate was 7.1% (28/394), 2.8% (10/359), 3.7% (7/187) and 6.8% (12/177), respectively. #*vs*. 6.0-6.9%, P=0.007; *vs. 6.0-6.9%, P=0.028. There were no differences between the other groups.

Causes of Death

In total, 57 patients died. The causes of death were infection, stroke, cardiovascular disease complicated by heart failure, diabetic nephropathy complicated by renal failure, lung cancer, a stress ulcer complicated by hemorrhage and cirrhosis complicated by hemorrhage. The proportion of each cause of death is shown in Figure **2**.

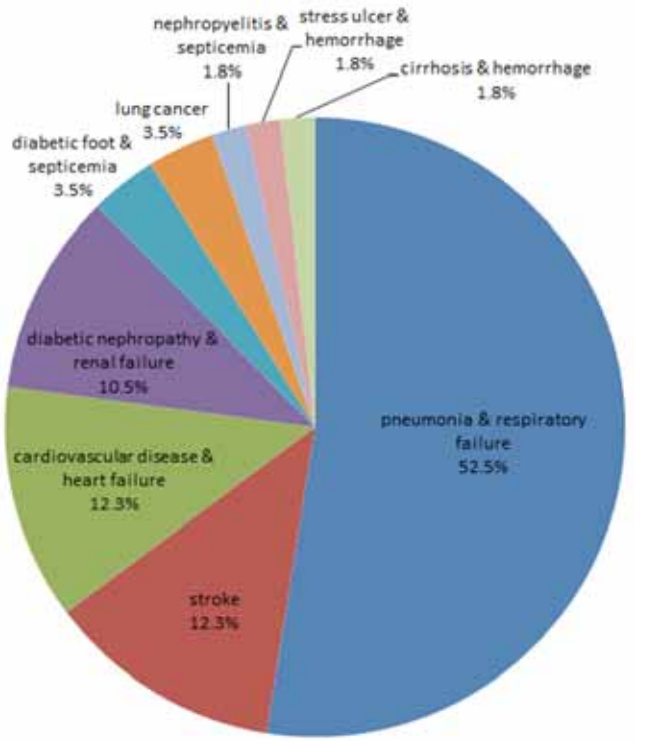

Figure 2: Proportion of all-cause death in diabetic patients admitted for severe hypoglycemia.

The causes of death included infection (n=33), stroke (n=7), cardiovascular disease complicated by heart failure (n=7), diabetic nephropathy complicated by renal failure (n=6), lung cancer (n=2), a stress ulcer complicated by hemorrhage (n=1) and cirrhosis complicated by hemorrhage (n=1).

DISCUSSION

Our study showed that the mortality rate of diabetic patients with severe hypoglycemia was different for patients with different HbA1c levels. The mortality rates for patients with HbA1c<6.0% and HbA1c≥8.0% were approximately 2-2.5 times that of patients with an HbA1c level of 6.0-6.9% and 7.0-7.9%. Generally, a U-shaped association was observed between the mortality rates and HbA1c levels. This U-shape relationship was also observed in other diabetes trials. A recent retrospective cohort study found a U-shaped association between survival and HbA1c [9]. In this study, patients with the lowest HbA1c levels (median 6.4%) were at a 52% increased risk of all-cause mortality relative to patients with a median HbA1c of 7.5%. In addition, patients in the highest HbA1c group (median HbA1c 10.5%) were at a 79% increased relative risk of mortality, with the lowest hazard ratio at an HbA1c level of 7.5% [9]. Another population study of patients admitted to hospital for acute myocardial infarction indicated that individuals with glucose levels at the extreme ends of the spectrum (high and low) had

higher mortality rates at hospital admission and at both 30 days and one year after the event compared with those who had normal blood glucose levels [10]. This U-shaped curve was present for individuals with and without clinically recognized diabetes [10]. In Colayco's study, patients with type 2 diabetes who achieved mean HbA1c levels of ≤6% or who failed to reduce their HbA1c to <8.0% over a 3-year period were at increased risk for cardiovascular events compared with patients who had mean HbA1c levels 6.0-8.0% [11]. In a retrospective cohort study in patients aged ≥60 years with type 2 diabetes, the risk of any end point (complication or death) also had a U-shaped relationship with HbA1c [12].

Why did severe hypoglycemia patients with lower and higher HbA1c have a higher mortality rate? Patients with HbA1c levels >8.0% were associated with a higher average glucose level, and severe hypoglycemia is an "unexpected" result. This "unexpected" result was associated with multiple metabolic disorders, such as long-term hyperglycemia, glucose excursion, severe hypoglycemia and infection in this survey. This was consistent with results of the ACCORD trial, which showed that rapid reduction of HbA1c by approximately 2% in participants entering the trial was a risk factor for death in the intensive treatment arm [13]. In contrast, in the ADVANCE trial, HbA1c was reduced to the target more gradually, which is thought to play a role in achieving a low death rate [14]. In contrast to "unexpected" severe hypoglycemia in patients with HbA1c>8.0%, severe hypoglycemia in patients with HbA1c<6% was "expected". HbA1c<6.0% was also associated with multiple metabolic disorders such as frequent hypoglycemia, severe hypoglycemia [3], and this level may increase mortality by impairing autonomic function, the adrenocorticotropin response and corticosteroid system [15, 16]. The risk of death is higher in patients with these two conditions (HbA1c>8.0% and <6.0%) compared with patients who had an HbA1c level of 6.0%-8.0%.

In our study, most of the patients died of co-morbidity; only four (18.5%) patients died of cardiovascular disease and heart failure. Hypoglycemia can cause death in type 1 diabetes [4]. However, associations between hypoglycemia and mortality do not establish a causal connection [4]. In the ACCORD trial, 74 of the patients who died had experienced at least one hypoglycemic episode requiring assistance, and only 1 patient died of severe hypoglycemia [6]. More recently, the co-morbidity of hypoglycemia has been increasingly emphasized. In the recent ADVANCE trial of patients with diabetes, Zoungas *et al*. noted that hypoglycemia was associated with an increased risk of death, and also with an increased risk of non-cardiac adverse events, including disorders of the digestive system, respiratory system, and the skin [17]. Severe hypoglycemia was associated with all-cause and cardiovascular mortality and also with non-cardiovascular mortality in type 2 diabetes. Thus, severe hypoglycemia might be a direct cause of death or it might be a marker of vulnerability to another cause of death [17]. Based on available evidence, severe hypoglycemia does not appear to directly lead to death or cardiovascular events and it is likely a marker for more severe illness and co-morbidity burden [18]. Although a discrete hypoglycemic episode may not be an immediate contributor to death in the clinical practice setting, susceptibility to hypoglycemia may predict an increased risk of death [6].

A limitation of our study is that 25% of the patients were not tested for HbA1c. Another limitation is that we did not correct the confounding factors (age, gender, comorbidities) for limited sample size. These may affect the mortality rate estimation.

In summary, our results indicate that there is a U-shape relationship between HbA1c and all-cause mortality rate in diabetic patients admitted for severe hypoglycemia. Severe hypoglycemia may predict an increased risk of death in patients with lower and higher HbA1c.

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REFERENCES

[1] Hypoglycemia in the Diabetes Control and Complications Trial. The Diabetes Control and Complications Trial Research Group. Diabetes 1997; 46: 271-86. http://dx.doi.org/10.2337/diab.46.2.271

[2] Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998; 352: 837-53. http://dx.doi.org/10.1016/S0140-6736(98)07019-6

[3] Cryer PE. The barrier of hypoglycemia in diabetes. Diabetes 2008; 57: 3169-76. http://dx.doi.org/10.2337/db08-1084

[4] Cryer PE. Death during intensive glycemic therapy of diabetes: mechanisms and implications. Am J Med 2011; 124: 993-6. http://dx.doi.org/10.1016/j.amjmed.2011.08.008

[5] ACCORD Study Group, Gerstein HC, Miller ME, Genuth S, *et al*. Long-term effects of intensive glucose lowering on cardiovascular outcomes. N Engl J Med 2011; 364: 818-28. http://dx.doi.org/10.1056/NEJMoa1006524

[6] Bonds DE, Miller ME, Bergenstal RM, *et al*. The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. BMJ 2010; 340: b4909. http://dx.doi.org/10.1136/bmj.b4909

[7] Investigators N-SS, Finfer S, Liu B, *et al*. Hypoglycemia and risk of death in critically ill patients. N Engl J Med 2012; 367: 1108-18. http://dx.doi.org/10.1056/NEJMoa1204942

[8] Li WG, He XL, Zhang T, *et al*. Hemoglobin A(1c) proportion, mortality rate, and risk factors for death in diabetic patients with severe hypoglycemia: a multicenter retrospective survey over ten years. Diabetes Res Clin Pract 2011; 93: 17-20. http://dx.doi.org/10.1016/j.diabres.2011.02.025

[9] Currie CJ, Peters JR, Tynan A, *et al*. Survival as a function of HbA(1c) in people with type 2 diabetes: a retrospective cohort study. Lancet 2010; 375: 481-9. http://dx.doi.org/10.1016/S0140-6736(09)61969-3

[10] Kosiborod M, Rathore SS, Inzucchi SE, *et al*. Admission glucose and mortality in elderly patients hospitalized with acute myocardial infarction: implications for patients with and without recognized diabetes. Circulation 2005; 111: 3078-86. http://dx.doi.org/10.1161/CIRCULATIONAHA.104.517839

[11] Colayco DC, Niu F, McCombs JS, Cheetham TC. A1C and cardiovascular outcomes in type 2 diabetes: a nested case-control study. Diabetes Care 2011; 34: 77-83. http://dx.doi.org/10.2337/dc10-1318

[12] Huang ES, Liu JY, Moffet HH, John PM, Karter AJ. Glycemic control, complications, and death in older diabetic patients: the diabetes and aging study. Diabetes Care 2011; 34: 1329-36. http://dx.doi.org/10.2337/dc10-2377

[13] Action to Control Cardiovascular Risk in Diabetes Study G, Gerstein HC, Miller ME, Byington RP, *et al*. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008; 358: 2545-59. http://dx.doi.org/10.1056/NEJMoa0802743

[14] Skyler JS, Bergenstal R, Bonow RO, *et al*, Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA diabetes trials: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. Diabetes Care 2009; 32: 187-92. http://dx.doi.org/10.2337/dc08-9026

[15] Adler GK, Bonyhay I, Failing H, Waring E, Dotson S, Freeman R. Antecedent hypoglycemia impairs autonomic cardiovascular function: implications for rigorous glycemic control. Diabetes 2009; 58: 360-6. http://dx.doi.org/10.2337/db08-1153

[16] Keller-Wood ME, Shinsako J, Dallman MF. Inhibition of the adrenocorticotropin and corticosteroid responses to hypoglycemia after prior stress. Endocrinology 1983; 113: 491-6. http://dx.doi.org/10.1210/endo-113-2-491

[17] Zoungas S, Patel A, Chalmers J, *et al*. Severe hypoglycemia and risks of vascular events and death. N Engl J Med 2010; 363: 1410-8. http://dx.doi.org/10.1056/NEJMoa1003795

[18] Lipska KJ, Kosiborod M. Hypoglycemia and adverse outcomes: marker or mediator? Rev Cardiovasc Med 2011; 12: 132-5.

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