JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
ORIGINAL ARTICLE

Hypoglycemia and glycemic variability are associated with mortality in non-intensive care unit hospitalized infectious disease patients with diabetes mellitus

Soichi Takeishi*, Akihiro Mori, Hiroki Hachiya, Takayuki Yumura, Shun Ito, Takashi Shibuya, Shintaro Hayashi, Nobutoshi Fushimi, Noritsugu Ohashi, Hiromi Kawai

Department of Endocrinology and Diabetes, Ichinomiyanishi Hospital, Ichinomiya, Japan

Keywords
Glycemic variability, Hypoglycemia, Mortality

***Correspondence**
Soichi Takeishi
Tel.: +81-586-48-0077
Fax: +81-586-48-0038
E-mail address: souichi19811225@yahoo.co.jp

J Diabetes Investig 2016; 7: 429–435

doi: 10.1111/jdi.12436

ABSTRACT

Aims/Introduction: We aimed to identify factors – glycemic control, reactive inflammatory biomarkers or vital signs – associated with mortality in diabetic patients admitted to hospital for various infections (non-intensive care unit).

Materials and Methods: We retrospectively analyzed the cases of 620 diabetic patients admitted to hospital for various infections (non-intensive care unit) who underwent glucose monitoring >3 times per day. We extracted data regarding reactive inflammatory biomarkers and vital signs recorded on day 1 of hospital stay, and data on bacteremia and hypoglycemia status, glycemic variability (GV; coefficient of variation and standard deviation) and mean glucose concentrations during the entire hospital stay. Univariate and stepwise multivariate logistic regression analyses were carried out to determine the association between these factors and mortality.

Results: The mortality rate was 10.1%. Reactive inflammatory biomarkers, vital signs and bacteremia were not associated with mortality. According to the results of the adjusted analysis, hypoglycemia showed a significant positive association with mortality, increasing death risk by 266% (odds ratio [OR] 2.66, 95% confidence interval [95% CI] 1.22–5.83; $P = 0.0006$). High coefficient of variation and standard deviation values were significantly associated with increased mortality, increasing death risk by 18% (OR 1.18, 95% CI 1.01–1.38; $P = 0.03$) and 9% (OR 1.09, 95% CI 1.01–1.18; $P = 0.03$), respectively. Mean glucose concentrations were also significantly associated with mortality, increasing death risk by 5% (OR 1.05, 95% CI 1.02–1.08; $P = 0.0008$).

Conclusions: Glycemic indices (especially hypoglycemia and GV), rather than reactive inflammatory biomarkers or vital signs, were associated with mortality in non-intensive care unit diabetes mellitus patients with infections.

INTRODUCTION

Recently, large clinical studies have shown that hypoglycemia is strongly associated with prognosis in patients with diabetes mellitus[1,2]. Furthermore, hypoglycemia is associated with mortality in patients with acute pathological conditions in the intensive care unit (ICU)[3–6] and in non-ICU hospitalized diabetes patients[7]. Glycemic variability (GV) is also thought to be associated with mortality in ICU patients[4,8] and in non-ICU hospitalized patients with acute pathological conditions[9].

Conversely, C-reactive protein (CRP) and arterial oxygen saturation (SpO_2) have been reported to be prognostic factors of pneumonia[10,11]. Furthermore, reactive inflammatory biomarkers and vital signs are associated with mortality in some infectious diseases[12–14], wherein glycemic control is thought to be compromised[15,16] and associated with mortality[17,18].

Received 18 July 2015; revised 28 August 2015; accepted 23 September 2015

Thus, glycemic control, reactive inflammatory biomarkers and vital signs could be associated with prognosis in patients with infectious diseases. However, which factors – glycemic control, reactive inflammatory biomarkers or vital signs – are most frequently associated with mortality in diabetic patients admitted to hospital for various infections (non-ICU) remains unclear. In the present study, we investigated the association between all of these factors and mortality in non-ICU diabetes mellitus patients with infectious diseases who underwent interventions for glycemic control.

MATERIALS AND METHODS

Study design and patient selection

The present study retrospectively analyzed hospital records of 38,367 patients during a 5-year period from 2009 to 2014.

The study was approved by the institutional review board of Ichinomiyanishi Hospital, Japan. All of the patient data extracted were anonymized, and informed consent of the patients was not required.

We selected diabetic patients admitted to hospital for various infections (non-ICU) and who underwent glucose monitoring >3 times per day. Patients with long durations of hospital stay (>90 days) and those who underwent very few sessions of glucose monitoring (<6 times in total) were excluded. Blood glucose concentrations were measured in capillary blood obtained by finger prick using a point-of-care device (ACCU-CHEK Aviva; Roche Diabetes Care GmbH, Indianapolis, IN, USA). Mortality was defined as in-hospital death.

Outcomes and statistical analysis

We extracted data regarding the age, sex, body-mass index (BMI), glycosylated hemoglobin concentration, reactive inflammatory biomarkers (i.e., white blood cell [WBC] count and CRP concentrations) and vital signs (i.e., body temperature [BT], systolic blood pressure, diastolic blood pressure, heart rate [HR] and SpO_2) on day 1 of hospital stay. We defined the presence of bacteremia if it persisted during the entire hospital stay. We evaluated the presence of underlying etiology of infection, besides diabetes, on day 1 of hospital stay. Hypoglycemia was defined as a blood glucose level of <70 mg/dL on any test carried out in the hospital. Hypoglycemia, GV (standard deviation [SD][19,20] and coefficient of variation [CV])[21,22] and mean glucose concentrations were determined from all the glycemic data collected during the entire hospital stay. We determined whether the patient had been taking any antidiabetic agents before hospital admission. We analyzed the association of these factors (explanatory variables) with mortality (response variable) by using a univariate logistic regression analysis. Using a stepwise multivariate logistic regression analysis, we further analyzed the association of the factors (explanatory variables) that were significantly associated with mortality, as determined using the univariate logistic regression analysis, with mortality (response variable). A *P*-value of <0.05 was considered statistically significant. Data are shown as medians (interquartile range).

RESULTS

Patient characteristics

In total, 620 patients (377 men, 243 women) who underwent intervention for glycemic control were included in the present study. The number of patients in each infectious disease category was as follows: pneumonia 341 (55.5%), urinary tract infections 80 (12.9%), gastrointestinal infections 38 (6.1%), biliary tract infections 77 (12.4%) and other infections, including surgical infections, 84 (13.5%). A total of 21 patients (3.4%) showed bacteremia. An underlying etiology of infection (underlying etiology), besides diabetes, was found in 203 patients (32.7%). In total, 54,876 values of glucose concentrations were analyzed. The number of glucose readings of the study patients was 4.4 (3.5–5.4) per day and 71 (50–108) during the hospitalization. Table 1 shows patient characteristics on day 1 of hospital stay and during the entire hospital stay.

Primary outcomes

In the univariate analysis, among all of the data collected on day 1 of hospital stay, sex, glycosylated hemoglobin concentration, reactive inflammatory biomarkers (WBC count and CRP concentration), vital signs (BT, systolic blood pressure, diastolic blood pressure, HR and SpO_2) and underlying etiology were not associated with mortality. However, age was significantly associated with increased mortality, and increased the risk of death by 3% (odds ratio [OR] 1.03, 95% confidence interval [95% CI] 1.01–1.06; $P = 0.01$). A low BMI value was also significantly associated with increased mortality, and increased the risk of death by 16% (OR 0.85, 95% CI 0.78–0.91; $P < 0.0001$). On the contrary, according to the results of the analysis of the data collected during the entire hospital stay, hypoglycemia showed a significant positive association with mortality, and increased the risk of death by 313% (OR 3.13, 95% CI 1.82–5.41; $P < 0.0001$). Similarly, a high CV was significantly associated with increased mortality, and increased the risk of death by 5% (OR 1.05, 95% CI 1.02–1.07; $P = 0.0001$). A high SD value was also associated with mortality, and increased the risk of death by 3% (OR 1.03, 95% CI 1.02–1.04; $P < 0.0001$), so high mean glucose concentration increased the risk of death by 2% (OR 1.02, 95% CI 1.01–1.02; $P < 0.0001$). Bacteremia was not associated with mortality. Use of an antidiabetic agent before hospital admission was not associated with mortality (Table 2).

After stepwise multivariate adjustment, age was eliminated from the list of explanatory variables. A low BMI value was significantly associated with increased mortality, and increased the risk of death by 12% (OR 0.88, 95% CI 0.81–0.95; $P = 0.002$). Hypoglycemia showed a significant positive association with mortality, and increased the risk of death by 266% (OR 2.66, 95% CI 1.22–5.83; $P = 0.0006$). Similarly, a high CV was significantly associated with increased mortality, and increased the risk of death by 18% (OR 1.18, 95% CI 1.01–1.38; $P = 0.03$). A high SD value was also associated with mortality, and increased the risk of death by 9% (OR 1.09, 95% CI 1.01–1.18; $P = 0.03$),

Table 1 | Characteristics of patients

n (men/women)	620 (377/243)
Type 1 diabetes/type 2 diabetes (*n*)	4/616
Pneumonia, *n* (%)	341 (55.0)
Urinary tract infection, *n* (%)	80 (12.9)
Gastrointestinal infection, *n* (%)	38 (6.1)
Biliary tract infection, *n* (%)	77 (12.4)
Surgical infection etc., *n* (%)	84 (13.5)
Age (years)	79.0 (71.0–85.0)
BMI (kg/m^2)	22.1 (19.0–24.9)
HbA1c, NGSP (%)	6.9 (6.4–7.9)
HbA1c, IFCC (mmol/mol)	51.9 (46.5–62.8)
WBC (mg/dL)	10400 (7,700–14,400)
CRP (mg/dL)	8.1 (2.8–16.0)
BT (°C)	37.0 (36.6–37.5)
SBP (mmHg)	124 (107–142)
DBP (mmHg)	68 (59–78)
HR (b.p.m.)	87.5 (77.0–98.0)
SpO2 (%)	96.0 (94.0–98.0)
No. blood measurements	
Per day	4.4 (3.5–5.4)
During the hospitalization	71 (50–108)
Bacteremia, *n* (%)	21 (3.4)
Underlying etiology, *n* (%)	203 (32.7)
Mean glucose level (mg/dL)	162.6 (135.4–188.8)
SD (mg/dL)	48.6 (33.0–66.7)
CV (%)	29.3 (21.7–36.9)
Hypoglycemia, *n* (%)	128 (20.6)
Length of stay (days)	17.0 (10.0–30.0)
Mortality, *n* (%)	64 (10.3)
Prehospital antidiabetic agent	
Sulfonylurea agent, *n* (%)	208 (33.5)
Metformin, *n* (%)	129 (20.8)
Thiazolidinediones, *n* (%)	92 (14.8)
α-Glucosidase inhibitor, *n* (%)	136 (21.9)
Insulin, *n* (%)	90 (14.5)
DPP-4 inhibitors, *n* (%)	230 (37.1)
GLP-1 receptor agonists, *n* (%)	12 (1.9)
Rapid-acting insulin	33 (5.3)
secretagogue, *n* (%)	
SGLT-2 inhibitor, *n* (%)	0 (0)
Insulin regimen in the hospital	19 (3.0)
Insulin sliding scale, *n* (%)	400 (64.5)
Basal–bolus, *n* (%)	38 (6.1)
Basal insulin only, *n* (%)	13 (2.1)
Other, *n* (%)	19 (3.1)
Not receiving any insulin treatment, *n* (%)	150 (24.2)

Data are shown as median (interquartile range). Hypoglycemia is defined as any documented in-hospital episode of glucose <70 mg/dL. BMI, body mass index; BT, body temperature, CRP, C-reactive protein; CV, coefficient of variation; DBP, diastolic blood pressure; DPP, dipeptidyl peptidase; GLP, glucagon-like peptide; HbA_{1c}, glycosylated hemoglobin; HR, heart rate; NGSP, National Glycohemoglobin Standardization Program; SBP, systolic blood pressure; SD, standard deviation; SGLT, sodium glucose co-transporter; SpO2, arterial oxygen saturation; Underlying etiology, underlying etiology of infection besides diabetes; WBC, white blood cell.

Table 2 | Relationship between the factors (glycemic control, reactive inflammatory biomarkers and vital signs) and mortality. (*n* = 620)

Variable	Mortality	
	OR (95% CI)	*P*-value
Age (years)	1.03 (1.01–1.06)	0.01
Male (*n*)	1.71 (0.96–3.02)	0.07
BMI (kg/m^2)	0.85 (0.78–0.91)	<0.0001
HbA1c, NGSP (%)	0.85 (0.69–1.05)	0.13
WBC (mg/dL)	1.00 (1.00–1.00)	0.11
CRP (mg/dL)	1.01 (0.98–1.04)	0.47
BT (°C)	0.81 (0.56–1.18)	0.28
SBP (mmHg)	1.01 (1.00–1.02)	0.06
DBP (mmHg)	1.02 (1.00–1.04)	0.06
HR (b.p.m.)	1.01 (0.99–1.02)	0.46
SpO2 (%)	1.10 (0.98–1.23)	0.09
Bacteremia	2.03 (0.66–6.20)	0.21
Underlying etiology	1.58 (0.93–2.67)	0.09
Mean glucose level (mg/dL)	1.02 (1.01–1.02)	<0.0001
SD (mg/dL)	1.03 (1.02–1.04)	<0.0001
CV (%)	1.05 (1.02–1.07)	0.0001
Hypoglycemia	3.13 (1.82–5.41)	<0.0001
Sulfonylurea agent	0.89 (0.51–1.55)	0.68
Metformin	0.51 (0.24–1.11)	0.09
Thiazolidinediones	0.93 (0.44–1.96)	0.85
α-Glucosidase inhibitor	0.63 (0.31–1.28)	0.20
Insulin	1.77 (0.93–3.35)	0.08
DPP-4 inhibitors	0.88 (0.51–1.51)	0.63
GLP-1 receptor agonists	1.00 (1.00–1.00)	1.00
Rapid-acting insulin secretagogue	0.86 (0.26–0.91)	0.81

Data were analyzed with univariate logistic regression analysis. BMI, body mass index; BT, body temperature; CI, confidence interval; CRP, C-reactive protein; CV, coefficient of variation; DBP, diastolic blood pressure; DPP, dipeptidyl peptidase; GLP, glucagon-like peptide; HbA_{1c}, glycosylated hemoglobin; HR, heart rate; NGSP, National Glycohemoglobin Standardization Program; OR, odds ratio; SBP, systolic blood pressure; SD, standard deviation; SGLT, sodium glucose co-transporter; SpO2, arterial oxygen saturation; Underlying etiology, underlying etiology of infection besides diabetes; WBC, white blood cell.

so high mean glucose concentration increased the risk of death by 5% (OR 1.05, 95% CI 1.02–1.08; $P = 0.0008$; Table 3).

Relationship of the factors collected during the entire hospital stay with hypoglycemia

According to the results of the univariate analysis, bacteremia and mean glucose concentration were not associated with hypoglycemia. A high CV was significantly associated with increased hypoglycemia, and increased the risk of death by 16% (OR 1.16, 95% CI 1.13–1.19; $P < 0.0001$). A high SD value was also associated with increased hypoglycemia, and increased the risk of death by 4% (OR 1.04, 95% CI 1.03–1.05; $P < 0.0001$; Table 4).

After stepwise multivariate adjustment, a high CV was significantly associated with increased hypoglycemia, and increased

Table 3 | Relationship between mortality and the factors that were significantly associated with mortality (adjusted). (n = 620)

Variable	Mortality	
	OR (95% CI)	*P*-value
BMI (kg/m^2)	0.88 (0.81–0.95)	0.002
Mean glucose level (mg/dL)	1.05 (1.02–1.08)	0.0008
SD (mg/dL)	1.09 (1.01–1.18)	0.03
CV (%)	1.18 (1.01–1.38)	0.03
Hypoglycemia, *n* (%)	2.66 (1.22–5.83)	0.01
R^2	0.22	
Significance		<0.0001

Data were analyzed with stepwise multivariate logistic regression analysis. Age was eliminated from the list of explanatory variables. BMI, body mass index; CI, confidence interval; CV, coefficient of variation; OR, odds ratio; SD, standard deviation.

Table 4 | Relationship between the factors collected during the entire hospital stay and hypoglycemia. (n = 620)

Variable	Hypoglycemia	
	OR (95% CI)	*P*-value
Bacteremia	1.14 (0.41–3.14)	0.81
Mean glucose level (mg/dL)	1.00 (1.00–1.01)	0.48
SD (mg/dL)	1.04 (1.03–1.05)	<0.0001
CV (%)	1.16 (1.13–1.19)	<0.0001

Data were analyzed with univariate logistic regression analysis. CI, confidence interval; CV, coefficient of variation; OR, odds ratio; SD, standard deviation.

the risk of death by 25% (OR 1.25, 95% CI 1.19–1.32; $P < 0.0001$). A high SD value was also associated with increased hypoglycemia, and increased the risk of death by 4% (OR 1.04, 95% CI 1.02–1.06; $P = 0.0004$; Table 5).

Determination of SD and CV cut-off values, which have the highest prediction ability for hypoglycemia, by using receiver operating characteristic analysis

Regarding SD, when the cut-off value was 58.3 mg/dL, which has the highest prediction ability, the sensitivity was 70% and the specificity was 72%. The area under the curve (AUC) for hypoglycemia was 0.76 (95% CI 0.72–0.81; $P < 0.0001$).

Regarding CV, when the cut-off value was 32.2%, which has the highest prediction ability, the sensitivity was 83% and the specificity was 71%. The AUC for hypoglycemia was 0.85 (95% CI 0.81–0.88; $P < 0.0001$; Figure 1).

Comparison of study participants stratified by the risk of mortality

Table 6 shows stratification of study participants according to the hypoglycemia status and GV. Study participants were stratified by whether hypoglycemia was present or not. Study participants were also stratified by whether GV was above the cut-off value or not, as this value has the highest predictive ability of hypoglycemia status using receiver operating characteristic analysis (CV 30%, SD 60 mg/dL).

Table 5 | Relationship between hypoglycemia and the factors that were significantly associated with hypoglycemia (adjusted). (n = 620)

Variable	Hypoglycemia	
	OR (95% CI)	*P*-value
SD (mg/dL)	1.04 (1.02–1.06)	0.0004
CV (%)	1.25 (1.19–1.32)	<0.0001
R^2	0.41	
Significance		<0.0001

Data were analyzed with stepwise multivariate logistic regression analysis. CI, confidence interval; CV, coefficient of variation; OR, odds ratio; SD, standard deviation.

When study participants were stratified by hypoglycemia status and CV, the mortality rates of participants in CV categories 3 and 4 were significantly higher (414 and 345%, respectively) than in CV category 1 (OR 4.14, 95% CI 1.06–16.21; $P = 0.04$; OR 3.45, 95% CI 1.83–6.52; $P = 0.0001$, respectively). The mortality rate of participants in CV category 2 was not significantly higher than that of participants in CV category 1.

When study participants were stratified by hypoglycemia status and SD, the mortality of the participants in SD category 4 was significantly higher (462%) than in CV category 1 (OR 4.62, 95% CI 2.40–8.90; $P < 0.0001$). The mortality rates of participants in CV categories 2 and 3 were not significantly higher than that of participants in CV category 1 (Table 7).

DISCUSSION

The results of the present study suggest that increased hypoglycemia and high CV value, SD value, and mean glucose concentrations, were significantly associated with increased mortality in the case of non-ICU diabetes mellitus patients with infectious diseases who underwent interventions for glycemic control. However, reactive inflammatory biomarkers and vital signs on day 1 of hospital stay were not associated with mortality.

As previously reported, in the case of patients with infectious diseases, the following clinical measures serve as prognostic factors at the time of admission: CRP concentration and SpO_2 in pneumonia[10,11]; BT, HR and WBC count in urinary tract infections[12]; BT, blood pressure and WBC count in cholangitis[13]; and HR and WBC count in cholecystitis[14]. In contrast, hyperglycemia in patients hospitalized for community-acquired pneumonia was a predictor of death[23]. The present study results suggest that glycemic control intervention, rather than the aforementioned prognostic factors, is associated with mortality. Thus, appropriate glycemic control is necessary in the case of non-ICU patients with infections, as in the case of ICU patients, and has great clinical importance.

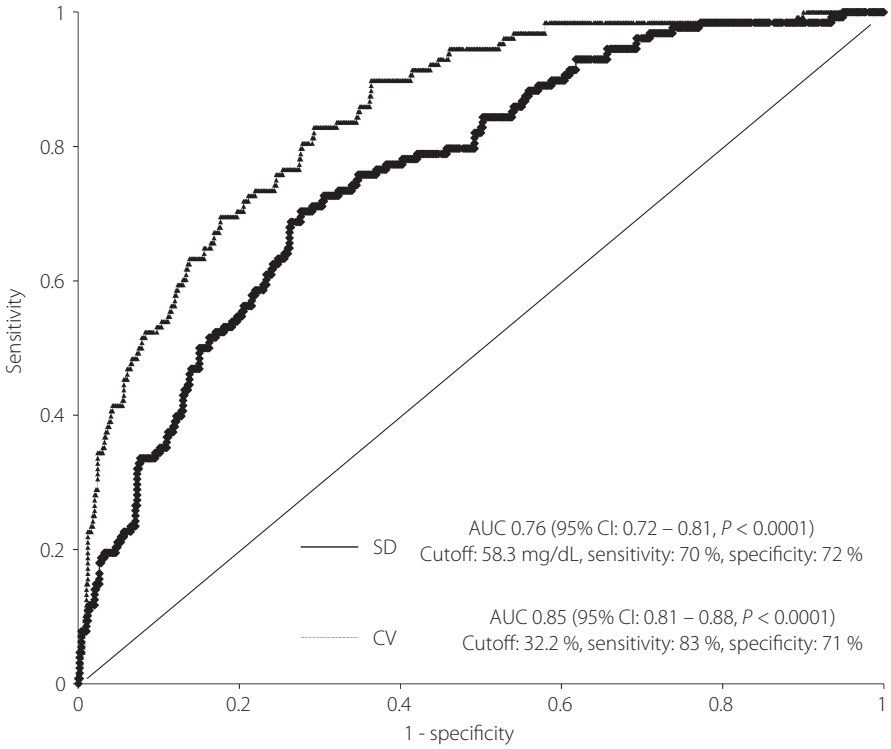

Figure 1 | Receiver operating characteristic curves for hypoglycemia in standard deviation (SD) and coefficient of variation (CV). Regarding SD, when the cut-off value was 58.3 mg/dL, which has the highest prediction ability, the sensitivity was 70% and the specificity was 72%. The area under the curve (AUC) for hypoglycemia was 0.76 (95% confidence interval [CI] 0.72–0.81; $P < 0.0001$). Regarding CV, when the cut-off value was 32.2%, which has the highest prediction ability, the sensitivity was 83% and the specificity was 71%. The AUC for hypoglycemia was 0.85 (95% CI 0.81–0.88; $P < 0.0001$).

Table 6 | Stratified study subjects by hypoglycemia status and glycemic variability

	CV <30% (*n*)	CV >30% (*n*)	Total
CV and hypoglycemia			
Hypoglycemia absent (*n*)	311 (CV category 1)	181 (CV category 2)	492
Hypoglycemia present (*n*)	44 (CV category 3)	84 (CV category 4)	128
Total	324	296	620
	SD <60 mg/dL (*n*)	SD >60 mg/dL (*n*)	Total
SD and hypoglycemia			
Hypoglycemia absent (*n*)	363 (SD category 1)	129 (SD category 2)	492
Hypoglycemia present (*n*)	44 (SD category 3)	84 (SD category 4)	128
Total	407	213	620

CV, coefficient of variation; SD, standard deviation.

As previously reported, hypoglycemia is associated with mortality, and the underlying mechanism for this association is considered to involve catecholamine that is secreted in surplus quantities in hypoglycemia, causing cardiac load[24,25]. In contrast, hypoglycemia is associated with the severity of sepsis: secretion of glucagon from the pancreas and gluconeogenesis in the liver decrease when severe sepsis occurs, causing multiple organ failure[26]. In the present study, increased hypoglycemia, but not bacteremia, was significantly associated with increased mortality in non-ICU diabetes mellitus patients with infectious diseases. Therefore, we elucidated which cause hypoglycemia – multiple organ failure caused by severe sepsis or glycemic control interventions. We examined which are associated with hypoglycemia – bacteremia or glycemic control interventions. The results showed that bacteremia and mean glucose concentrations were not associated with hypoglycemia. High CV and SD values were associated with increased hypoglycemia. Therefore, we believe that increased hypoglycemia was not caused by bacteremia; however, GV was found to be associated with increased mortality in the present study. Next, we investigated the association between the risk of hypoglycemia and the degree of GV in the present study. The results suggest that the risk of hypoglycemia increases significantly if GV is >60 mg/dL and GV/glucose concentration is >30%. Thus, treatment should be preferably adjusted in non-ICU diabetes mellitus patients with infectious diseases whose GV is <60 mg/dL and GV/glucose concentration is <30%.

Table 7 | Comparison between categories on risk of mortality

	OR (95% CI)	*P*-value
CV and hypoglycemia		
CV category 1	Reference	Reference
CV category 2*	1.34 (0.68–2.64)	0.4
CV category 3*	4.14 (1.06–16.21)	0.04
CV category 4*	3.45 (1.83–6.52)	0.0001
SD and hypoglycemia		
SD category 1	Reference	Reference
SD category 2*	1.80 (0.90–3.61)	0.10
SD category 3*	2.33 (0.89–6.09)	0.08
SD category 4*	4.62 (2.40–8.90)	<0.0001

*In comparison with category 1. CI, confidence interval; CV, coefficient of variation; OR, odds ratio; SD, standard deviation.

GV has also been reported to be associated with mortality[27]. GV increases oxidative stress, and thereby causes vascular endothelial dysfunction[28]. Therefore, oxidative stress is considered to be associated with increased mortality. In fact, the concentration of protein kinase C-β, which is an index of oxidative stress, increases when glucose concentration decreases; that is, from hyperglycemia status to normoglycemia status[29]. In addition, the mean amplitude of glycemic excursion was reported to be significantly associated with 8-isoprostaglandin F2α concentration in the urine, which is an index of oxidative stress in patients with type 2 diabetes[30].

We suggested that increased hypoglycemia and GV were significantly associated with increased mortality in the present study. Therefore, we stratified study participants by hypoglycemia status and GV to investigate the combined effect of hypoglycemia and high GV on the risk of mortality. These results suggest that the combined effect of hypoglycemia and high GV increase the risk of mortality more strongly than either individually.

Hyperglycemia has also been shown to increase oxidative stress and mortality rate[17,18]. Increased oxidative stress causes insulin resistance and promotes a repetitive cycle, thereby increasing the severity of hyperglycemia[31]. In any case, glycemic instability is likely to be associated with mortality, and the present results support this observation.

Our data suggest that glycemic control interventions after hospital admission, rather than reactive inflammatory biomarkers or vital signs on admission, which were previously reported as prognostic factors, was associated with prognosis in non-ICU diabetes mellitus patients with infectious diseases. Thus, glycemic control interventions after hospital admission, rather than the severity of infectious diseases on admission, dictates prognosis in non-ICU diabetes mellitus patients with infectious diseases. In this study, we did not investigate changes in reactive inflammatory biomarkers or vital signs after admission, and therefore, we could not determine associations between glycemic control and these parameters in infectious diseases. Impaired glycemic control has been reported to be associated with severe infectious diseases[15], sand therefore, poor glycemic control after admission would lead to poor prognosis of infectious diseases. Not only intervention for glycemic control, but also highly intensive care is necessary in the case of patients with infectious disease who show poor glycemic control.

The results of the present study suggest that increased hypoglycemia and high CV value, SD value, and mean glucose concentrations during the entire hospital stay, rather than reactive inflammatory biomarkers or vital signs on day 1 of hospital stay, were associated with increased mortality in non-ICU diabetes mellitus patients with infectious diseases. As a result of this study, we believe that glycemic control should be carried out with the goal of avoiding clinical glycemic instability. However, the present study was limited by certain factors. First, this study was carried out in a single center; second, interventions for glycemic control were not carried out according to a unified protocol; third, reactive inflammatory biomarkers and vital signs were evaluated only according to data collected on day 1 of hospital stay; and finally, underlying etiology and cause of death varied among patients. Prospective studies with continuous glucose monitoring to further investigate the relationship between glycemic control and clinical outcomes are necessary.

ACKNOWLEDGMENT

This work was supported in part by the Ichinomiyanishi Hospital. Parts of this study have been presented in poster presentation at the 75th Scientific Sessions of the American Diabetes Association, Boston, Massachusetts, from 5 to 9 June 5 2015.

DISCLOSURE

The authors declare no conflict of interest.

REFERENCES

1. Currie JC, Peters RJ, Tynan A, *et al.* Survival as a function of HbA1c in people with type 2 diabetes: a retrospective cohort study. *Lancet* 2010; 375: 481–489.
2. Khunti K, Davies M, Majeed A, *et al.* Hypoglycemia and risk of cardiovascular disease and all-cause mortality in insulin-treated people with type 1 and type 2 diabetes: a cohort study. *Diabetes Care* 2015; 38: 316–322.
3. Kalfon P, Le Manach Y, Ichai C, *et al.* Severe and multiple hypoglycemic episodes are associated with increased risk of death in ICU patients. *Crit Care* 2015; 19: 153.
4. Bagshaw SM, Bellomo R, Jacka MJ, *et al.* The impact of early hypoglycemia and blood glucose variability on outcome in critical illness. *Crit Care* 2009; 13: 91.
5. Krinsley JS, Grover A. Severe hypoglycemia in critically ill patients: risk factors and outcomes. *Crit Care Med* 2007; 35: 2262–2267.
6. Egi M, Bellomo R, Stachowski E, *et al.* Hypoglycemia and outcome in critically ill patients. *Mayo Clin Proc* 2010; 85: 217–224.

7. Turchin A, Matheny ME, Shubina M, *et al.* Hypoglycemia and clinical outcomes in patients with diabetes hospitalized in the general ward. *Diabetes Care* 2009; 32: 1153–1157.
8. Ley SC, Kindgen-Milles D. Variability of blood glucose concentration and short-term mortality in critically ill patient. *Anaesthesist* 2007; 56: 820–821.
9. Mendez CE, Mok KT, Ata A, *et al.* Increased glycemic variability is independently associated with length of stay and mortality in noncritically ill hospitalized patients. *Diabetes Care* 2013; 36: 4091–4097.
10. Chalmers JD, Singanayagam A, Hill AT. C-reactive protein is an independent predictor of severity in community-acquired pneumonia. *Am J Med* 2008; 121: 219–225.
11. Watanabe A, Yanagihara K, Kohno S, *et al.* Multicenter survey on hospital-acquired pneumonia and the clinical efficacy of first-line antibiotics in Japan. *Intern Med* 2008; 47: 245–254.
12. Johansen TE, Botto H, Cek M, *et al.* Critical review of current definitions of urinary tract infections and proposal of an EAU/ESIU classification system. *Int J Antimicrob Agents* 2011; 38: 64–70.
13. Csendes A, Diaz JC, Burdiles P, *et al.* Risk factors and classification of acute suppurative cholangitis. *Br J Surg* 1992; 79: 655–658.
14. Yacoub WN, Petrosyan M, Sehgal I, *et al.* Prediction of patients with acute cholecystitis requiring emergent cholecystectomy: a simple score. *Gastroenterol Res Pract.* 2010; 2010: 901739.
15. Bagdade JD, Stewart M, Walters E. Impaired granulocyte adherence: a reversible defect in host defense in patients with poorly controlled diabetes. *Diabetes* 1978; 27: 677–681.
16. Robinson LE, van Soeren MH. Insulin resistance and hyperglycemia in critical illness: role of insulin in glycemic control. *AACN Clin Issues* 2004; 15: 45–62.
17. Sano T, Umeda F, Hashimoto T, *et al.* Oxidative stress measurement by *in vivo* electron spin resonance spectroscopy in rats with streptozotocin-induced diabetes. *Diabetologia* 1998; 41: 1355–1360.
18. Latham R, Lancaster AD, Covington JF, *et al.* The association of diabetes and glucose control with surgical-site infections among cardiothoracic surgery patients. *Infect Control Hosp Epidemiol* 2001; 22: 607–612.
19. Krinsley JS. Glycemic variability: a strong independent predictor of mortality in critically ill patients. *Crit Care Med* 2008; 36: 3008–3013.
20. Egi M, Bellomo R, Stachowski E, *et al.* Variability of blood glucose concentration and short-term mortality in critically ill patients. *Anesthesiology* 2006; 105: 244–252.
21. Rodbard D. Clinical interpretation of indices of quality of glycemic control and glycemic variability. *Postgrad Med* 2011; 123: 107–118.
22. Siegelaar SE, Holleman F, Hoekstra JB, *et al.* Glucose variability; does it matter? *Endocr Rev* 2010; 31: 171–182.
23. Lepper PM, Ott S, Nüesch E, *et al.* Serum glucose levels for predicting death in patients admitted to hospital for community acquired pneumonia: prospective cohort study. *BMJ* 2012; 344: 3397.
24. Cryer PE. Severe hypoglycemia predicts mortality in diabetes. *Diabetes Care* 2012; 35: 1814–1816.
25. Gerich JE. Hypoglycaemia and counterregulation in type 2 diabetes. *Lancet* 2000; 356: 1946–1947.
26. Ssekitoleko R, Jacob ST, Banura P, *et al.* Hypoglycemia at admission is associated with inhospital mortality in Ugandan patients with severe sepsis. *Crit Care Med* 2011; 39: 2271–2276.
27. Peter JV, Mani RK. Association between glycemic variability and mortality: How robust is the evidence? *Indian J Crit Care Med* 2014; 18: 269–270.
28. Zhao G, Seng J, Yan B, *et al.* Diagnosis and surgical treatment of ruptured aneurysm in sinus of Valsalva. *Chin Med J (Engl)* 2003; 116: 1047–1050.
29. Quagliaro L, Piconi L, Assaloni R, *et al.* Intermittent high glucose enhances apoptosis related to oxidative stress in human umbilical vein endothelial cells: the role of protein kinase C and NAD(P)H-oxidase activation. *Diabetes* 2003; 52: 2795–2804.
30. Monnier L, Mas E, Ginet C, *et al.* Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. *JAMA* 2006; 295: 1681–1687.
31. Samuel VT, Shulman GI. Mechanisms for insulin resistance: common threads and missing links. *Cell* 2012; 148: 852–871.