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Original article

Impact of admission glycemia and glycosylated hemoglobin A1c on long-term clinical outcomes of non-diabetic patients with acute coronary syndrome

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ABSTRACT

Background: Admission glucose levels have proven to be a predictor in patients with acute myocardial infarction and elevated glycosylated hemoglobin A1c (HbA1c) is associated with an increased risk of cardiovascular disease, even in patients without diabetes. However, the effect of both admission glucose and HbA1c levels on clinical outcomes in non-diabetic patients with acute coronary syndrome (ACS) has not been fully elucidated. We evaluated the combined effect of admission glucose and HbA1c values on long-term clinical outcomes in non-diabetic patients with ACS treated with percutaneous coronary intervention (PCI).

Methods and results: This was an observational study of 452 consecutive non-diabetic patients with ACS who underwent PCI between January 1997 and December 2006. The patients were assigned to four groups according to the median values of admission glucose and HbA1c. The primary endpoint comprising a composite of all-cause death and non-fatal MI was compared among the four groups. The primary endpoint occurred in 13.3% of the participants during a median follow-up period of 4.7 years. The cumulative incidence rate of primary endpoint significantly differed among the groups ($p = 0.048$). Multivariable Cox regression analysis showed that the combination of elevated admission glucose and HbA1c was independently associated with long-term clinical outcomes.

Conclusions: Combined admission glucose and HbA1c values were independently associated with clinical outcomes in non-diabetic patients with ACS treated with PCI.

Introduction

Hyperglycemia on admission in patients with acute myocardial infarction (AMI) is a negative predictor of short- and long-term clinical outcomes [1–5]. Hyperglycemia is also associated with poor clinical outcomes among non-diabetic patients and the risk of mortality is higher in hyperglycemic patients without diabetes than those with diabetes [6–11]. Glycosylated hemoglobin A1c (HbA1c) is a marker of long-term glycemic control and elevated HbA1c is associated with an increased risk of cardiovascular diseases in patients with diabetes [12]. Moreover, HbA1c is also associated with all-cause mortality and cardiovascular disease even in the absence of diabetes [13,14]. Both admission glucose and HbA1c values are associated with clinical outcomes in patients with AMI [15]. However, the combined effect of admission glucose and HbA1c on clinical outcomes in an Asian population with acute coronary syndrome (ACS) remains unknown. Therefore, we evaluated the combined effect of admission glucose and HbA1c values on long-term clinical outcomes in non-diabetic patients with ACS treated with percutaneous coronary intervention (PCI).

Methods

Study population

This observational study analyzed consecutive non-diabetic patients with ACS who were treated with PCI at Juntendo University Hospital (Tokyo, Japan) between January 1997 and December 2006. The patients were assigned to four groups according to a median

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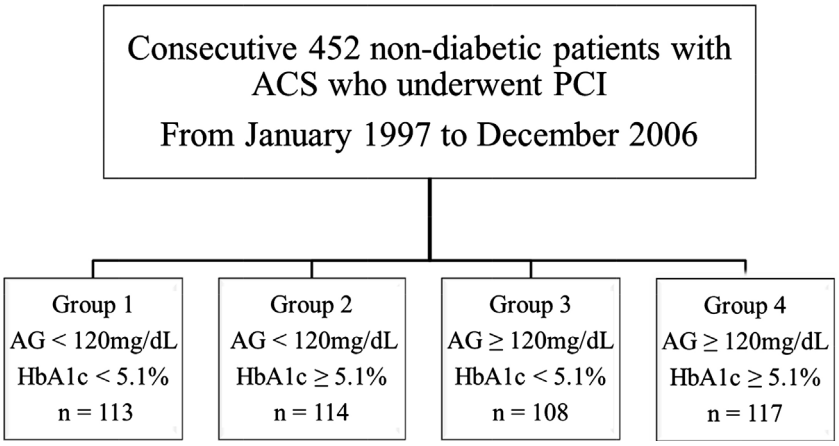

Fig. 1. Flow chart of study population. The study population included 452 consecutive non-diabetic patients with ACS who underwent PCI between January 1997 and December 2006. ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; AG, admission glucose level; HbA1c, glycosylated hemoglobin A1c.

admission glucose value of 120 mg/dL and HbA1c expressed as a National Glycohemoglobin Standardization Program (NGSP) value of 5.6%. Groups 1 and 4 comprised patients with lower and higher admission levels of both components, respectively, Group 2 comprised those with lower admission glucose and higher HbA1c, and Group 3 comprised higher admission glucose and lower HbA1c (Fig. 1). Demographic data including age, gender, body mass index (BMI), coronary risk factors, medication use, and comorbidities were collected.

Clinical outcomes

The primary endpoint was a composite of all-cause death and non-fatal MI. Information regarding the clinical outcomes was collected during clinical visits, telephone interviews, or from the referring physician. Our institutional review board approved the protocol of this study, which was performed in accordance with the principles established in the Declaration of Helsinki and our institutional ethics policy.

Definitions

We defined ACS as unstable angina pectoris (UAP), non-ST segment elevation myocardial infarction (NSTEMI), or STEMI. UAP was defined as having angina at rest or in an accelerating pattern with negative cardiac biomarkers, with or without electrocardiogram (ECG) changes indicative of myocardial ischemia (for example, ST segment depression, or transient elevation, or new T wave inversion). Myocardial infarction was defined as an increase ($\leq$2-fold) in serum creatine kinase (CK) and troponin T positivity. Patients were considered non-diabetic if they met the following criteria: (i) their medical records did not include a history of diabetes; (ii) they were not under treatment with anti-diabetic agents or insulin; (iii) they had HbA1c (NGSP) values < 6.5%. We converted HbA1c [Japan Diabetes Society (JDS)] values to HbA1c (NGSP) units using the following equation: NGSP (%) = 1.02 × JDS (%) + 0.25% [16]. Hypertension was defined as systolic blood pressure $\geq$ 140 mmHg and diastolic blood pressure $\geq$ 90 mmHg or under treatment with anti-hypertensive medications. Dyslipidemia was defined as triglyceride levels $\geq$ 150 mg/dL, low-density lipoprotein cholesterol levels $\geq$ 140 mg/dL, high-density lipoprotein cholesterol levels < 40 mg/dL, or under treatment for dyslipidemia. We defined current smokers as individuals who smoked at the time of admission or had quit within one year before the study period. Renal failure was defined as an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2 calculated using the modification of diet in renal disease equation modified with a Japanese coefficient using baseline serum creatinine [17].

Statistical analysis

Continuous variables are expressed as means with standard deviation. Categorical variables are expressed as counts and ratios (%). Continuous variables were compared using a one-way analysis of variance followed by post hoc analysis using Dunnett's test for multiple comparisons. Group 1, which comprised patients with lower admission glucose and HbA1c values, served as a control group in the post hoc analysis. Categorical variables were compared using the χ^2 test or Fisher's exact probability test. Unadjusted cumulative event rates were estimated using the Kaplan–Meier method and compared among groups using the log-rank test. Hazard ratios and 95% confidence intervals for each variable were calculated using a Cox proportional hazards model. Predictors of long-term clinical outcomes were identified using a multivariable Cox regression analysis. Variables with $p < 0.1$ in the univariable Cox regression analysis were included in the multivariable model. A value of $p < 0.05$ was considered to indicate statistical significance. All data were analyzed using JMP version 9.0 for Windows (SAS Institute, Cary, NC, USA).

Results

We analyzed data from 452 consecutive non-diabetic patients with ACS who underwent PCI from January 1997 to December 2006 over a median follow-up period of 4.7 (interquartile range, 2.2–7.5) years. The baseline characteristics of the patients are shown in Table 1. Only the prevalence of dyslipidemia and prior PCI significantly differed among the groups. Peak CK values and the prevalence of STEMI were higher and left ventricular ejection fraction (LVEF) was lower in Groups 3 and 4 than in Group 1 (Table 2). The prevalence of multi-vessel coronary disease (MVD) was higher in Groups 2 and 4, which included patients with higher HbA1c values. The primary endpoint occurred in 13.3% of the study participants during the follow-up period. The rates of all-cause, cardiac, and non-cardiac deaths were 10.6%, 4.4%, and 6.2%, respectively, whereas that of non-fatal MI was 3.5% (Table 3). The cumulative incidence of the primary endpoint significantly differed among the groups (log-rank test, $p = 0.048$; Fig. 2). Group 4 (elevated admission glucose and HbA1c values), age, gender, BMI, LVEF, eGFR, Hb, statin use, and MVD were associated with all-cause mortality and non-fatal MI in the univariable Cox regression analysis. Elevated

Table 1
Baseline characteristics.

	Group 1 (*N* = 113) both lower	Group 2 (*N* = 114) higher HbA1c	Group 3 (*N* = 108) higher AG	Group 4 (*N* = 117) both higher	*p*-Value
Age	62.2 ± 11.5	63.8 ± 11.6	65.0 ± 11.3	65.7 ± 11.7	0.1
Male, *n* (%)	102 (89.5)	94 (82.5)	83 (77.6)	92 (78.6)	0.07
BMI, kg/m^2	23.8 ± 3.9	24.0 ± 3.3	24.0 ± 3.6	23.6 ± 3.5	0.7
Hypertension, *n* (%)	65 (57.0)	76 (66.7)	70 (65.4)	69 (59.0)	0.3
Dyslipidemia, *n* (%)	63 (55.3)	78 (68.4)	44 (41.1)	68 (58.6)	<0.001
Smoking, *n* (%)	42 (36.8)	29 (25.4)	35 (32.7)	27 (23.1)	0.08
Family history, *n* (%)	32 (28.1)	28 (24.6)	30 (28.0)	32 (27.4)	0.9
Renal dysfunction, *n* (%)	26 (23.6)	27 (24.6)	27 (26.5)	30 (27.8)	0.9
Hemodialysis, *n* (%)	1 (1.5)	2 (3.3)	4 (7.1)	1 (1.6)	0.3
Prior MI, *n* (%)	7 (6.1)	12 (10.5)	4 (3.7)	14 (12.0)	0.08
Prior PCI, *n* (%)	14 (12.3)	25 (21.9)	3 (2.8)	11 (11.7)	<0.001
Prior CABG, *n* (%)	4 (3.5)	7 (6.1)	0 (0)	7 (6.0)	0.06

AG, admission glucose; HbA1c, hemoglobin A1C; BMI, body mass index; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary bypass graft.

Table 2
Clinical characteristics.

	Group 1 (*N* = 113) both lower	Group 2 (*N* = 114) higher HbA1c	Group 3 (*N* = 108) higher AG	Group 4 (*N* = 117) both higher	*p*-Value
SBP, mmHg	135.6 ± 20.4	135.7 ± 27.6	134.3 ± 22.7	131.1 ± 27.6*	0.5
DBP, mmHg	74.4 ± 11.7	73.9 ± 14.5	75.0 ± 14.0	73.6 ± 15.8	0.9
LDL-C, mg/dL	116.6 ± 35.6	120.9 ± 29.5	120.0 ± 29.0	119.5 ± 39.5	0.8
HDL-C, mg/dL	46.2 ± 14.5	44.2 ± 12.3	43.9 ± 10.1	45.1 ± 11.0	0.5
TG, mg/dL	107.7 ± 58.2	122.2 ± 52.3	114.1 ± 68.0	120.4 ± 95.9	0.4
Hb, g/dL	13.6 ± 1.9	13.5 ± 1.7	13.7 ± 1.7	13.8 ± 2.0	0.7
AG, mg/dL	102.0 ± 11.8	104.7 ± 9.7	147.7 ± 28.6*	160.9 ± 48.6*	<0.001
HbA1c, %	4.8 ± 0.4	5.5 ± 0.2*	4.9 ± 0.2	5.5 ± 0.2*	<0.001
LVEF, %	62.0 ± 13.8	60.4 ± 12.4	55.6 ± 12.1*	55.1 ± 14.2*	<0.001
BNP, pg/mL	196.7 ± 75.1	133.1 ± 66.4	298.5 ± 73.1	213.7 ± 58.2	0.4
CRP, mg/dL	0.98 ± 2.3	1.3 ± 2.3	1.5 ± 2.9	0.6 ± 1.8	0.07
eGFR, mL/min/1.73 m^2	74.4 ± 21.1	71.3 ± 19.0	77.1 ± 24.3	75.2 ± 21.0	0.2
Creatine kinase, U/L (maximum)	1100.0 ± 1667.3	690.9 ± 1216.9	2288.6 ± 2040.0*	2522.0 ± 2559.0*	<0.001
Medication, *n* (%)					
Statin	53 (46.5)	53 (46.5)	38 (35.5)	42 (36.2)	0.2
ACE-I/ARB	71 (62.3)	75 (65.8)	81 (75.7)	83 (71.6)	0.1
β-Blocker	46 (40.4)	42 (36.8)	42 (39.3)	53 (45.7)	0.6
Culprit vessel, *n* (%)					0.2
LAD	61 (53.5)	57 (50.0)	55 (51.9)	58 (50.0)	
LCX	14 (12.3)	22 (19.3)	19 (17.9)	12 (10.3)	
RCA	35 (30.7)	31 (27.2)	32 (30.2)	40 (34.2)	
LMT	0 (0)	0 (0)	0 (0)	2 (1.7)	
Multivessel disease, *n* (%)	46 (40.4)	58 (50.9)	33 (30.8)	52 (44.4)	0.02
Type of ACS, *n* (%)					<0.001
UAP	47 (41.2)	39 (34.2)	8 (7.8)	18 (15.5)	
NSTEMI	21 (18.4)	26 (22.8)	19 (17.9)	20 (17.2)	
STEMI	46 (40.4)	49 (43.0)	79 (74.5)	78 (67.2)	

SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; TG, triglyceride; AG, admission glucose; HbA1c, hemoglobin A1C; LVEF, left ventricular ejection fraction; BNP, brain natriuretic peptide; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; LMT, left main trunk; ACS, acute coronary syndrome; UAP, unstable angina pectoris; (N)STEMI, (non-)ST elevation myocardial infarction.

* Statistically significant value calculated by Dunnett' s test was marked with asterisk.

Table 3
Long-term clinical events.

	Group 1 (*N* = 113) lower AG, lower HbA1c	Group 2 (*N* = 114) lower AG, higher HbA1c	Group 3 (*N* = 108) higher AG, lower HbA1c	Group 4 (*N* = 117) higher AG, higher HbA1c
All-cause death	8 (7.0)	10 (8.8)	9 (8.4)	18 (15.7)
CVD	2 (1.8)	3 (2.6)	5 (4.7)	10 (8.6)
Non-CVD	6 (5.3)	7 (6.1)	4 (3.7)	8 (6.8)
Non-fatal MI	2 (1.8)	2 (1.8)	5 (4.7)	8 (6.8)

AG, admission glucose; HbA1c, hemoglobin A1C; CVD, cardiovascular disease; MI, myocardial infarction.

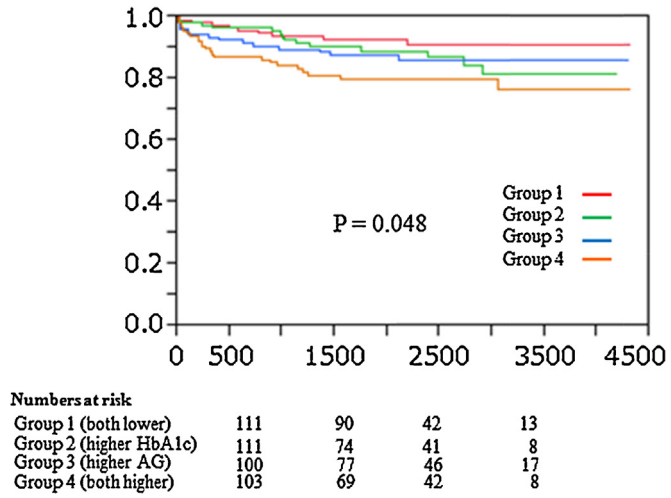

Fig. 2. Kaplan–Meier curves for all-cause death and non-fatal MI. The cumulative incidence rate of primary endpoint significantly differed among the groups MI, myocardial infarction; AG, admission glucose level; HbA1c, glycosylated hemoglobin A1c.

admission glucose and HbA1c values remained significant after adjustment for variables (Table 4).

Discussion

The present study demonstrated that elevated admission glucose combined with HbA1c values were associated with poor long-term clinical outcomes in non-diabetic patients with ACS treated with PCI. The association remained significant even after adjustment for other independent variables.

Hyperglycemia on admission is considered to represent a stress response to acute diseases whereas there remains a possibility that hyperglycemia is a reflection of impaired glucose tolerance. The prognostic value of admission hyperglycemia for diabetic patients with AMI has been established [1,2,4,5]. Ishihara et al. identified admission hyperglycemia as a predictor of in-hospital mortality after AMI in an Asian population [3]. Moreover, the risk of mortality is higher in non-diabetic patients with hyperglycemia than in diabetic patients [6–11]. The value of HbA1c is related to risk for cardiovascular disease in patients with diabetes [12] and it is significantly associated with all-cause mortality and cardiovascular disease, even in non-diabetic patients [13,14]. A recent report showed an association between both admission glucose and HbA1c, and a poor prognosis in non-diabetic patients with AMI [15]. That study found a 10% mortality rate during a mean follow-up period of 3.3 years and their multivariable analysis demonstrated that elevated HbA1c was associated with long-term mortality (HR 1.2, 95% CI 1.0–1.3, $p < 0.01$). The present study differed from the previous reports in that we determined the combined effect of high admission glucose and HbA1c values on long-term clinical outcomes in non-diabetic Asian patients with ACS.

Several potential mechanisms might explain our findings. Hyperglycemia might have disturbed endothelial function through a reduction in the release of nitric oxide and increased superoxide production in vessel walls [18–21]. Higher serum glucose increases vascular smooth muscle cell proliferation and migration [20,22]. These phenomena could lead to atherosclerosis via endothelial dysfunction. Hyperglycemia is a reflection of impaired insulin secretion that is related to lipolysis and increase of circulating free fatty acids [1]. An excess of free fatty acids has toxicity to ischemic myocardium through an increase of myocardial oxygen consumption, resulting in a development of ventricular arrhythmias and impaired myocardial contractility [23]. Thus, it is conceivable that admission hyperglycemia could be a negative prognostic factor among patients with cardiovascular diseases. In fact, 30-day mortality was significantly higher in our study population with higher admission glucose levels (HR 1.01, 95% CI 1.001–1.020, $p = 0.035$). This population had higher peak CK levels, a higher prevalence of STEMI and reduced LVEF, which might have affected the clinical outcomes. Previous reports that have demonstrated the prognostic impact of peak CK and reduced LVEF on clinical outcomes in patients with MI [24–28] could support our findings. We identified a relationship between admission HbA1c and MVD, which is a predictor of poor clinical outcomes in patients with MI [29–31]. Therefore, the high prevalence of MVD could be associated with poor clinical outcomes in patients with higher admission HbA1c values. Elevated HbA1c has been reported to be associated with the new onset of diabetes and future cardiovascular diseases in a non-diabetic general population [14]. Therefore, our study population with both higher admission glucose and HbA1c might have had glucose dysmetabolism with a high possibility of overt

Table 4
Univariable and multivariable Cox regression analysis for all-cause death and non-fatal myocardial infarction.

	Univariable			Multivariable		
	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Age, years	1.09	1.06–1.12	<0.0001	1.07	1.03–1.10	<0.0001
Male gender	0.79	0.44–1.53	0.47	2.14	1.06–4.63	0.03
Hypertension, yes	1.12	0.67–1.94	0.67			
Dyslipidemia, yes	0.84	0.50–1.40	0.50			
BMI, kg/m^2	0.85	0.79–0.92	<0.0001	0.92	0.84–0.99	0.04
LVEF, %	0.96	0.94–0.98	<0.0001	0.97	0.95–0.99	0.005
Hb, g/dL	0.77	0.68–0.87	<0.0001	0.81	0.67–0.96	0.02
eGFR, mL/min/1.73 m^2	0.98	0.96–0.99	0.006	0.99	0.98–1.01	0.29
Statin, yes	0.45	0.24–0.80	0.006	0.77	0.39–1.45	0.43
CRP	1.03	0.92–1.13	0.5			
STEMI	1.43	0.85–2.50	0.18			
Creatine kinase, U/L (maximum)	1.0	0.99–1.0001	0.14			
Multivessel disease, yes	1.76	1.06–2.96	0.03	1.72	0.98–3.07	0.06
HbA1c and AG (Group 1 as reference)						
Group 2 (higher HbA1c)	1.61	0.71–3.86	0.26	1.92	0.81–4.88	0.14
Group 3 (higher AG)	1.69	0.74–4.06	0.21	1.93	0.79–4.99	0.15
Group 4 (both higher)	2.77	1.32–6.31	0.006	2.65	1.17–6.58	0.02

HR, hazard ratio; 95% CI, 95% confidence interval; BMI, body mass index; LVEF, left ventricular ejection fraction; Hb, hemoglobin; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; STEMI, ST-elevation myocardial infarction; AG, admission glucose level.

diabetes, although we did not have data regarding a prevalence of overt diabetes during the follow-up period.

Limitations

The present study has several limitations. First, this was a single-center observational study including a relatively small sample size. Second, they did not undergo the oral glucose tolerance test (OGTT) to diagnose diabetes mellitus. Since we classified patients as non-diabetes with the criteria described in the Methods section, patients with undiagnosed diabetes might have been misclassified as non-diabetic. In addition, there were no considerations about impaired glucose tolerance or postprandial hyperglycemia which has been associated with increased risk for coronary artery disease [32,33], because we did not perform OGTT. Third, specific agents such as catecholamines that could affect glucose metabolism might be administered in a part of the study population. In addition, we did not aim to clarify the occurrence of diabetes mellitus among the patients during the study period. Moreover, patients with higher admission glucose and HbA1c did not undergo definite intervention to treat hyperglycemia. Thus, the significance of glycemic control for long-term clinical outcomes in this population was not elucidated.

Conclusions

The combination of high admission glucose and HbA1c levels was significantly associated with poor long-term clinical outcomes in non-diabetic patients with ACS treated with PCI. Careful observation might be required for the early detection of overt diabetes mellitus in such patients. Further study is needed to elucidate specific therapeutic strategies to prevent cardiovascular events occurring in non-diabetic patients with ACS who have elevated admission glucose and HbA1c values.

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