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Impact of Acute and Chronic Hyperglycemia on In-hospital Outcomes of Patients with Acute Myocardial Infarction

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Running title: Acute and chronic hyperglycemia in AMI

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Abstract

This study was undertaken to assess the impact of acute hyperglycemia (acute-HG) and chronic hyperglycemia (chronic-HG) on short-term outcomes in patients with acute myocardial infarction (AMI). This study consisted of 696 patients with AMI. Acute-HG was defined as admission plasma glucose ≥200 mg/dl and chronic-HG as HbA1c ≥6.5%. Acute-HG was associated with higher peak serum creatinine kinase (4,094 ± 4,594 vs. 2,526 ± 2,227 IU/l, p <0.001) and in-hospital mortality (9.8% vs. 1.6%, p <0.001). On the contrary, there was no significant difference in peak creatinine kinase (2,803 ± 2,661 vs. 2,940 ± 3,181 IU/l, p = 0.59) and mortality (3.3 vs. 3.7%, p = 0.79) between patients with chronic-HG and those without. Multivariable analysis showed that admission plasma glucose was an independent predictor of in-hospital mortality (odds ratio 1.15, 95% CI 1.05 to 1.27; p <0.001), but HbA1c was not. When only patients with acute-HG were analyzed, chronic-HG was associated with a significantly smaller infarct size (3,221 ± 3,001 vs. 5,904 ± 6,473 IU/l, p <0.001) and lower in-hospital mortality (5.5 vs. 18.9%, p = 0.01). In conclusion, these results suggested that acute-HG, but not chronic-HG, was associated with adverse short-term outcomes after AMI. Paradoxically, in patients with acute-HG, chronic-HG might abate the adverse effects of acute-HG.

Key words: acute hyperglycemia, chronic hyperglycemia, acute myocardial infarction

Introduction

It has been reported that hyperglycemia (HG) causes oxidative stress, enhances inflammation, induces apoptosis and activates coagulation, which deteriorate myocardial damage in the setting of ischemia. (1-3). In the clinical practice, admission plasma glucose is used as a measure of acute hyperglycemia (acute-HG) and hemoglobin A1c (HbA1c) for chronic hyperglycemia (chronic-HG). However, it remains unclear how acute-HG and chronic-HG affect short-term outcomes in patients with acute myocardial infarction (AMI). The purpose of the present study was to investigate impact of acute-HG and chronic-HG on short-term outcomes after AMI.

Methods

From January 2007 to June 2012, 760 consecutive patients who were admitted to National Cerebral and Cardiovascular Center of Japan within 48 hours after the onset of AMI were prospectively enrolled to the observational single-center registry and were retrospectively analyzed. In this registry, AMI was defined by a combination of 2 of the 3 followings; chest pain longer than 30 minutes, electrocardiographic signs and elevation of serum creatinine kinase more than twice the upper normal limit. Patients for whom laboratory data were lacking (n = 64) were excluded from the present study. Finally, this study consisted of the remaining 696 patients constituted the study

population with short-term clinical follow-up. The allocation of emergency coronary angiography and coronary intervention was determined by physician's decision. The study protocol was approved by the institutional review board of National Cerebral and Cardiovascular Center, and was conducted in accordance with regulations governing epidemiological studies issued by the Ministry of Health, Labor, and Welfare of Japan.

On admission, age, sex, body mass index and comorbidity such as hypertension, diabetes, dyslipidemia, smoker and previous myocardial infarction were recorded. Plasma glucose was obtained at the time of admission and HbA1c was during hospitalization. Serum creatinine kinase was measured every 3 hours until it reached peak value. Acute-HG was defined as admission plasma glucose ≥200 mg/dl (4). Chronic-HG was defined as HbA1c ≥6.5% (5). Chronic kidney disease is defined as estimated glomerular filtration rate ≤30 mL/min/1.73m^2 in this study.

Continuous data were shown as mean ± standard deviation. Continuous variables were compared by use of the *t* test and categorical variables with χ^2 statistics or Fisher exact test. Logistic regression analysis was used to obtain odds ratio (OR) and 95% confidence interval (CI) for in-hospital mortality. In multivariate analysis, the association between acute-HG and chronic-HG were adjusted for baseline variables, including age, sex, smoker, previous myocardial infarction, elapsed time, ST-elevation

myocardial infarction, Killip classification ≥2 and primary coronary intervention. Multivariate analysis was also performed when plasma glucose and HbA1c were analyzed as a continuous variable. P values <0.05 were considered statistically significant. All statistical analysis was performed using JMP® (version 11.0, SAS Inc.).

Results

This study consisted of 696 patients. 652 patients (94%) underwent emergency coronary angiography. Primary coronary intervention was performed in 606 patients (87%), mostly with stents (92%). Final Thrombolysis in Myocardial Infarction grade 3 flow was obtained in 553 patients (91%).

Acute-HG was found in 163 patients (23%). Table 1 shows the baseline characteristics of patients with and without acute-HG. Patients with acute-HG had significantly higher plasma glucose on admission (276 ± 75 vs. 139 ± 28 mg/dl, p <0.001) and HbA1c (7.2 ± 1.9 vs. 5.6 ± 0.8 %, p <0.001) than those without acute-HG. Acute-HG was associated with more diabetes, more chronic kidney disease, more Killip classification ≥2 and higher body mass index.

There were 212 (30%) patients with chronic-HG. The baseline characteristics of patients with chronic-HG and without chronic-HG were shown in Table 2. Both

admission plasma glucose and HbA1c were higher in patients with chronic-HG than without chronic-HG (223 ± 86 vs. 148 ± 52 mg/dl, p <0.001 and 7.5 ± 1.5 vs. 5.4 ± 0.3 %, p <0.001, respectively). Chronic-HG was associated with more diabetes and more dyslipidemia.

Peak creatinine kinase was obtained in 691 patients (99%). Patients with acute-HG had a significantly higher peak creatinine kinase than without acute-HG (p <0.001) (Figure 1A). There was no significant difference in peak creatinine kinase between in patients with chronic-HG and without chronic-HG (p = 0.59) (Figure 1A). In-hospital mortality rate was significantly higher in patients with acute-HG than in those without (p <0.001) (Figure 1B), but chronic-HG was not associated in-hospital mortality (p = 0.79) (Figure 1B).

In univariate analysis, acute-HG was associated with a 6-fold increase in in-hospital mortality risk (OR 6.34, 95% CI [2.8 to 15.3], p <0.001). When plasma glucose was analyzed as a continuous variable, an increase of 1mmol/L (18mg/dl) in plasma glucose was associated with an increase in mortality risk of 18% (OR 1.18, 95% CI [1.10 to 1.26], p <0.001). On the contrary, chronic-HG (OR 0.88, 95% CI [0.34-2.06], p = 0.79) and HbA1c (OR 1.14, 95% CI [0.85-1.43], p = 0.31) were not predictive factors of in-hospital mortality.

In multivariate analysis, acute-HG was independently associated with in-hospital mortality (OR 6.35, 95% CI [2.29 to 18.9], p <0.001), but chronic-HG was not (OR 0.47, 95% CI [0.15 to 1.37], p = 0.16). Analyzed as a continuous variable, plasma glucose was an independent predictor for in-hospital mortality (OR 1.21, 95% CI [1.09 to 1.35], p <0.001), but HbA1c was not (OR 0.85, 95% CI [0.57 to 1.20], p = 0.36).

Peak creatinine kinase and in-hospital mortality are shown in Figure 2 stratified according to acute-HG and chronic-HG. Acute-HG was associated with large infarct size and high in-hospital mortality in both patients with chronic-HG and those without chronic-HG. In 528 patients without acute-HG, there was no significant difference in peak creatinine kinase and in-hospital mortality between patients with and without chronic-HG. On the contrary, in 163 patients with acute-HG, chronic-HG was associated with smaller peak creatinine kinase and lower in-hospital mortality.

Discussion

The major findings of this study were, 1) acute-HG was associated with large infarct size and high in-hospital mortality in patients with AMI, but chronic-HG was not; 2) in patients with acute-HG, chronic-HG was paradoxically associated with small infarct size and low mortality after AMI.

As precious studies have reported (6-10), the current study showed that acute-HG is associated with larger infarct size and higher in-hospital mortality in patients with AMI. Although there had been debate as to whether acute-HG is causally related to poor outcome after AMI or is simply an epiphenomenon of the severe disease conditions, most recent studies have demonstrated that acute-HG is causally associated with further deterioration of myocardial damage and poor outcomes after reperfusion.

Acute-HG is observed not only in diabetic but also non-diabetic patients with AMI. Although earlier studies classified non-diabetic patients with acute-HG as pre-existing undiagnosed diabetes, recent studies have shown that acute-HG in non-diabetic patients does not represent pre-existing undiagnosed diabetes (11). In the thrombolysis era, it has been reported that diabetes and chronic glucose dysregulation, as assessed by HbA1c levels, are prognostic factors for in-hospital mortality in patients with AMI (12). However, recent studies have shown that diabetes is not associated with short-term outcomes after AMI in patients who underwent primary coronary intervention (9, 13, 14). In the current study, we also showed that chronic-HG assessed by HbA1c did not predict infarct size and in-hospital mortality in patients with AMI who were mostly treated with primary coronary intervention.

Several clinical and experimental studies have shown that acute increase of plasma glucose causes several unfavorable effects, including oxidative stress, inflammation, apoptosis, endothelial dysfunction and hyper-coagulation, that may contribute to the poor outcomes of patients with AMI. Esposito et al (1) reported that the plasma cytokine levels increased as the plasma glucose level increased during consecutive pulses of intravenous glucose but immediately returned to normal as plasma glucose returned to normal levels. Of note, when the first elevation in the blood glucose level was maintained by subsequent continuous intravenous glucose infusion, plasma cytokine concentrations gradually returned to normal levels, despite sustained high plasma glucose level. Apoptosis is also enhanced by intermittent, rather than constant, high glucose concentration (2).

In patients with AMI undergoing primary coronary intervention, Iwakura et al (15) have shown that no-reflow phenomenon assessed by contrast echocardiography was predicted by acute-HG but not by a history of diabetes or by HbA1c. Recently, Teraguchi et al (16) reported, using continuous glucose measurement and cardiac magnetic resonance imaging, that there was a significant negative relation between glucose fluctuation and myocardial salvage index. In addition, we have previously reported that acute-HG abolishes ischemic preconditioning that has potent endogenous

cardioprotective effect against myocardial ischemia (17). These findings suggest that acute elevation of plasma glucose (acute-HG), but not constant high glucose concentration (CHG), deteriorates myocardial damage and outcomes after AMI.

In this study, we showed that acute-HG was associated with large infarct size and high in-hospital mortality in both patients with chronic-HG and those without chronic-HG. In patients without acute-HG, peak creatinine kinase was small and mortality was low, regardless of the presence or absence of chronic-HG. Interestingly, chronic-HG was associated with small peak creatinine kinase and low mortality in patients with acute-HG. There are several possible mechanisms that may explain this paradoxical finding. The magnitude of acute glucose elevation may become small in patients with chronic-HG, because baseline glucose level should be high in these patients. Experimental studies have suggested that diabetic heart is paradoxically more resistant to ischemic insults. Decreased activity of sodium proton exchanger in diabetic myocardium may prevent reperfusion injury (18). Also, decreased glucose utilization observed in diabetic cells may be beneficial in a circumstance of high plasma glucose.

Results of previous studies that have investigated whether continuous insulin infusion to normalize the glucose level will improve the outcome of patients with AM are inconsistent (19, 20). Most of these studies consisted of patients with diabetes and/or

acute-HG. Because impact of acute-HG is more pronounced in patients without chronic-HG, glucose control to correct acute-HG may be more beneficial for patients without chronic-HG or diabetes. Further studies should be warranted into the appropriate management in patients with AMI and acute-HG in the contemporary intervention era.

This study has the limitations of all retrospective investigations. However, this study consisted of consecutive patients with AMI who received contemporary management, including primary coronary intervention in 87% of patients. A small sample size is another limitation of this study. Because of the nature of observational study, the cause-effect relation between plasma glucose and outcomes, and impact of acute management of plasma glucose on outcomes were not investigated.

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Figure Legends

Figure 1: Effects of acute-HG and chronic-HG on peak creatinine kinase and in-hospital mortality

(A) Patients with acute-HG had a significantly higher peak creatinine kinase than without acute-HG (4,094 ± 4,594 vs. 2,526 ± 2,227 IU/l, p <0.001). There was no significant difference in peak creatinine kinase between in patients with chronic-HG and without chronic-HG (2,803 ± 2,661 vs. 2,940 ± 3,181 IU/l, p = 0.585)

(B) In-hospital mortality rate was significantly higher in patients with acute-HG than in patients without (9.8% vs. 1.6%, p <0.001). There was no significant difference in mortality between patients with and without chronic-HG (3.3 vs. 3.7%, p = 0.79)

Figure 2: Effects of chronic-HG on peak creatinine kinase and in-hospital mortality in patients with acute-HG and in those without acute-HG

When only patients without acute-HG were analyzed, there was no significant difference in peak creatinine kinase (2,348 ± 2,156 vs. 2,572 ± 2,244 IU/l, p = 0.364) and in-hospital mortality (1.0 vs. 1.9%, p = 1.00) between patients with and those without chronic-HG. On the contrary, in patients with acute-HG, chronic-HG was

associated with smaller peak creatinine kinase (3,221 ± 3,001 vs. 5,904 ± 6,473 IU/L, p <0.001) and lower mortality (5.5 vs. 18.9%, p = 0.01).

Table 1
Baseline characteristics of patients with and without acute hyperglycemia

Variables	Acute Hyperglycemia		pValue
	Yes (n=163)	No (n=533)	
Age (yrs)	68.7 ± 11.9	67.4 ± 12.8	0.268
Men	72%	72%	0.921
Body mass index (kg/m^2)	24.4 ± 3.8	23.3 ± 3.7	0.002
Diabetes Mellitus	69%	24%	<0.001
Hypertension	72%	66%	0.214
Dyslipidemia	61%	54%	0.105
Smoker	32%	33%	0.964
Chronic kidney disease	48%	29%	<0.001
Previous myocardial infarction	9%	10%	0.881
ST elevation myocardial infarction	80%	84%	0.342
Anterior location	39%	39%	1.000
Killip class 2 to 4	35%	14%	<0.001
Elapsed time (hour)	7.1 ± 10.2	7.5 ± 9.7	0.701
Primary percutaneous coronary intervention	90%	86%	0.349
Medication before infarction			
Antiplatelet agent	21%	18%	0.494
Angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers	31%	22%	0.021
Calcium-channel blocker	27%	26%	0.919
Beta-blocker	12%	10%	0.562
Statin	23%	17%	0.066
Oral hypoglycemic agent	29%	8%	<0.001
Insulin	9%	2%	<0.001