Admission Hyperglycemia Is an Independent Predictor of Acute Kidney Injury in Patients With Acute Myocardial Infarction

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**Background:** Acute kidney injury (AKI) and acute hyperglycemia are associated with unfavorable outcomes. The impact of acute hyperglycemia on the development of AKI after acute myocardial infarction (AMI), however, remains unclear. This study was undertaken to assess the relationship between admission glucose and incidence of AKI after AMI.

**Methods and Results:** This study consisted of 760 patients with AMI admitted to the National Cerebral and Cardiovascular Center within 48 h after symptom onset. Blood sample was obtained on admission and repeated sampling was done at least every 1 or 2 days during the first week. AKI was diagnosed as increase in serum creatinine ≥0.3 mg/dl or ≥50% within any 48 h. Ninety-six patients (13%) had AKI during hospitalization for AMI, and these patients had higher in-hospital mortality than those without AKI (25% vs. 3%, P<0.001). Patients with AKI had higher plasma glucose (PG) on admission than those without (222 ±105 mg/dl vs. 166 ±69 mg/dl, P<0.001). The incidence of AKI increased as admission PG rose: 7% with PG <120 mg/dl; 9% with PG 120–160 mg/dl; 11% with PG 160–200 mg/dl; and 28% with PG >200 mg/dl (P<0.01). On multivariate analysis admission PG was an independent predictor of AKI (odds ratio, 1.10; 95% confidence interval: 1.03–1.18, P=0.02).

**Conclusions:** Admission hyperglycemia might have contributed to the development of AKI in patients with AMI. (Circ J 2014; 78: 1475–1480)

**Key Words:** Acute hyperglycemia; Acute kidney injury; Acute myocardial infarction

Acute kidney injury (AKI) is a complex disorder that occurs in a variety of conditions and is often associated with poor prognosis. Acute myocardial infarction (AMI) is one of the critical conditions in which AKI is likely to occur, because of its comorbid factors, hemodynamic instability or other renotoxic agents. Although it is often underrecognized, AKI is associated with adverse outcomes, including higher incidence of heart failure and mortality after AMI. Despite the recent recognition of the importance of AKI, the incidence of AKI factors contributing to AKI and its consequence in patients with AMI are not fully understood.

Recent studies have demonstrated the prognostic importance of acute hyperglycemia in patients with AMI. We have previously reported that high plasma glucose (PG) at the time of admission is linearly associated with increased in-hospital mortality in AMI patients. This finding is independent from a history of diabetes or hemoglobin A1c (HbA1c). The postulated mechanisms for the causal relationship between acute hyperglycemia and poor outcome after AMI include enhanced oxidative stress, exacerbated inflammation, apoptosis, endothelial dysfunction and activation of coagulation and platelet activity. Indeed, these are all factors that may exacerbate renal dysfunction in critical ill conditions and may cause AKI. In this study, we assessed the association between acute hyperglycemia and the development of AKI in patients with AMI.
Methods

Patients
From January 2007 to June 2012, 760 consecutive patients who were admitted to National Cerebral and Cardiovascular Center in Japan within 48 h after symptom onset were included into the retrospective observed registry of AMI at the National Cerebral and Cardiovascular Center. AMI was diagnosed on chest pain consistent with ongoing myocardial ischemia persisting >30 min and concomitant electrocardiographic changes. Serum creatine kinase was measured every 3–4 h for at least 24 h until it reached a peak, and the peak creatine kinase value had to be more than twice the normal upper limit.

Laboratory Data
Blood samples, including PG, creatinine and other baseline laboratory parameters were required to be obtained on admission. (Some parameters including HbA1c may be obtained days after admission.)

Blood sampling was repeated every 3–4 h until creatin...
Categorical data are reported as proportions and continuous data as mean ± SD. Statistical analysis was done with the chi-squared test for categorical variables, and t-test was used for continuous variables. Logistic regression analysis was used to obtain odds ratios (OR) and 95% confidence intervals (CI) for the development of AKI. In multivariate analysis, the association between admission PG and the development AKI was adjusted for age, and all predictors of AKI. Because HbA1c was not obtained in 50 patients (6.5%), 2 models of multivariate analysis were used. In the first model, age, hypertension, dyslipidemia, diabetes mellitus, Killip class, hemoglobin, estimated glomerular filtration rate (eGFR), creatinine, previous angina, previous PCI, primary PCI and use of aspirin and anti-hyperglycemic agent were adjusted. In the second model, HbA1c was added to these variables. We used JMP (version 10.0, SAS institute). A significance level of 0.05 was used and 2-tailed tests were applied.

Table 2. Models of In-Hospital Mortality

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
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<th>Multivariate</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P-value</td>
<td>OR (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>Admission plasma glucose (per 18 mg/dl)</td>
<td>1.11 (1.01–1.18)</td>
<td>&lt;0.001</td>
<td>1.04 (1.01–1.09)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AKI</td>
<td>10.7 (5.67–20.6)</td>
<td>&lt;0.001</td>
<td>3.5 (1.48–8.31)</td>
<td>0.004</td>
</tr>
<tr>
<td>Killip ≥2</td>
<td>24.9 (11.6–62.4)</td>
<td>&lt;0.001</td>
<td>10.2 (4.2–28.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR (ml · min⁻¹ · 1.73 m⁻²)</td>
<td>0.96 (0.94–0.97)</td>
<td>&lt;0.001</td>
<td>1.00 (0.99–1.02)</td>
<td>0.64</td>
</tr>
<tr>
<td>Hemoglobin (g/ml)</td>
<td>0.74 (0.65–0.84)</td>
<td>&lt;0.001</td>
<td>0.87 (0.74–1.02)</td>
<td>0.091</td>
</tr>
<tr>
<td>Age (per 10 years)</td>
<td>1.03 (1.01–1.06)</td>
<td>0.0061</td>
<td>1.00 (0.97–1.04)</td>
<td>0.71</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.71 (0.92–3.15)</td>
<td>0.09</td>
<td>1.98 (0.85–4.88)</td>
<td>0.12</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>4.05 (2.00–7.85)</td>
<td>0.002</td>
<td>2.27 (0.78–6.51)</td>
<td>0.13</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>4.24 (1.36–11.1)</td>
<td>0.016</td>
<td>1.1 (0.23–4.37)</td>
<td>0.91</td>
</tr>
<tr>
<td>Aspirin</td>
<td>3.24 (1.72–6.04)</td>
<td>0.004</td>
<td>2.43 (0.91–6.37)</td>
<td>0.071</td>
</tr>
</tbody>
</table>

CI, confidence interval; OR, odds ratio. Other abbreviations as in Table 1.

Figure 2. Incidence of acute kidney injury (AKI) in patients with acute myocardial infarction. The incidence of AKI increased as admission plasma glucose (PG) increased. There were 7% of 189 patients with PG <120 mg/dl; 9% of 281 patients with PG 120–160 mg/dl; 11% of 138 patients with PG 160–200 mg/dl; and 28% of 152 patients with PG >200 mg/dl (P<0.001).

Data Analysis

In the current study, we investigated the prevalence of AKI and admission hyperglycemia. Impacts of AKI and admission hyperglycemia on in-hospital mortality were also assessed. Finally, we evaluated factors that are related to the development of AKI, especially impact of admission hyperglycemia on renal function.

Categorical data are reported as proportions and continuous data as mean ± SD. Statistical analysis was done with the chi-squared test for categorical variables, and t-test was used for continuous variables. Logistic regression analysis was used to obtain odds ratios (OR) and 95% confidence intervals (CI) for the development of AKI. In multivariate analysis, the association between admission PG and the development AKI was adjusted for age, and all predictors of AKI. Because HbA1c was not obtained in 50 patients (6.5%), 2 models of multivariate analysis were used. In the first model, age, hypertension, dyslipidemia, diabetes mellitus, Killip class, hemoglobin, estimated glomerular filtration rate (eGFR), creatinine, previous angina, previous PCI, primary PCI and use of aspirin and anti-hyperglycemic agent were adjusted. In the second model, HbA1c was added to these variables. We used JMP (version 10.0, SAS institute). A significance level of 0.05 was used and 2-tailed tests were applied.
patients with PG 120–160 mg/dl; 11% of 138 patients with PG AKI was 7% of 189 patients with PG <120 mg/dl; 9% of 281 of AKI increased as admission PG increased. The incidence of between admission PG and the incidence of AKI. The incidence ± 69 mg/dl, \( P<0.001 \)).

Patients with AKI had higher PG on admission (222 ± 105 mg/dl vs. 166 ± 105 mg/dl \( P<0.001 \)).

Admission PG and AKI

Baseline characteristics of the study patients are listed in Table 1. Emergency coronary angiography was performed in 708 patients (93%) and primary PCI in 654 patients (86%). Among the entire 760 patients, AKI developed in 96 patients (13%). The demographic, clinical, and biochemical characteristics of the patients with and without AKI are listed in Table 1. There were significant differences in age, diabetes mellitus, Killip class ≥2, dyslipidemia, creatinine and eGFR, HbA1c, hemoglobin, and admission glucose between patients with AKI and those without. There was no significant difference in emergency angiography and primary PCI. Anti-hyperglycemic agent (oral hyperglycemic drug and/or insulin) were more frequently used in patients with AKI before AMI (Table 1).

Incidence of AKI in AMI Patients

In previous studies the incidence of AKI has ranged from 10% to 20% in AMI patients.6,19,20 The ACTION registry, which enrolled 59,970 patients with AMI who were mostly treated with primary PCI, reported that 16.1% of patients developed AKI during hospitalization.21 In the current study, the incidence of AKI was 13%, which is similar to these previous reports.

In the last decade, primary PCI has become the treatment of choice for patients with AMI, and number of patients who receive coronary angiography has been rapidly increasing. The contrast medium is nephrotoxic, and may cause acute tubular necrosis. This is termed ‘contrast-induced AKI (CI-AKI)’.5,21–23 There is a concern about the risk of CI-AKI for patients undergoing coronary angiography and primary PCI for AMI. In the present study, however, both emergency angiography and primary PCI were not associated with AKI in AMI patients. Consistent findings have been reported. Amin et al assessed the temporal trend in the use of PCI and the development of AKI in 31,532 patients with AMI. Interestingly, the incidence of AKI has progressively declined (from 26.6% in the year 2000 to 19.7% in 2008), as the use of PCI has progressively increased (from 32.1% in the year 2000 to 47% in 2008).6 Therefore, CI-AKI seems not to be the main cause of AKI in patients with AMI.

Results

The major findings of this study are: (1) AKI developed in 13% after AMI; (2) AKI was associated with in-hospital mortality after AMI; and (3) admission hyperglycemia was an independent risk factor for AKI in patients with AMI.

Discussion

Table 3. Models of Incidence of AKI

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th>Multivariate</th>
<th>Model 1</th>
<th>Multivariate</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P-value</td>
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</tr>
<tr>
<td>Admission plasma glucose (per 18 mg/dl)</td>
<td>1.11 (1.00–1.21)</td>
<td>&lt;0.001</td>
<td>1.18 (1.06–1.31)</td>
<td>0.002</td>
<td>1.10 (1.03–1.18)</td>
</tr>
<tr>
<td>Killip ≥2</td>
<td>5.95 (3.79–9.38)</td>
<td>&lt;0.001</td>
<td>3.4 (1.97–5.86)</td>
<td>&lt;0.001</td>
<td>3.49 (1.91–6.39)</td>
</tr>
<tr>
<td>eGFR (ml·min⁻¹·1.73m⁻²)</td>
<td>0.96 (0.95–0.97)</td>
<td>&lt;0.001</td>
<td>0.97 (0.96–0.98)</td>
<td>&lt;0.001</td>
<td>0.97 (0.96–0.98)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>0.55 (0.55–0.84)</td>
<td>0.006</td>
<td>0.51 (0.27–0.77)</td>
<td>0.003</td>
<td>0.37 (0.21–0.66)</td>
</tr>
<tr>
<td>Anti-hyperglycemic agent</td>
<td>2.18 (1.30–3.59)</td>
<td>0.002</td>
<td>1.16 (0.55–2.43)</td>
<td>0.69</td>
<td>1.05 (0.46–2.39)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.6 (1.66–3.95)</td>
<td>&lt;0.001</td>
<td>1.8 (0.92–3.34)</td>
<td>0.08</td>
<td>1.58 (0.73–3.29)</td>
</tr>
<tr>
<td>Age (per 10 years)</td>
<td>1.03 (1.02–1.06)</td>
<td>&lt;0.001</td>
<td>1.01 (0.99–1.03)</td>
<td>0.20</td>
<td>1.01 (0.99–1.04)</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>0.77 (0.70–0.84)</td>
<td>&lt;0.001</td>
<td>0.93 (0.83–1.04)</td>
<td>0.23</td>
<td>0.86 (0.75–0.98)</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>1.79 (0.98–3.14)</td>
<td>0.057</td>
<td>1.3 (0.56–2.91)</td>
<td>0.52</td>
<td>1.34 (0.52–3.33)</td>
</tr>
<tr>
<td>Emergency PCI</td>
<td>0.61 (0.36–1.08)</td>
<td>0.09</td>
<td>0.97 (0.47–1.91)</td>
<td>0.94</td>
<td>0.91 (0.40–1.92)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>1.54 (0.93–2.49)</td>
<td>0.081</td>
<td>1.47 (0.73–3.06)</td>
<td>0.28</td>
<td>1.86 (0.85–4.28)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.52 (0.94–2.53)</td>
<td>0.082</td>
<td>1.03 (0.57–1.92)</td>
<td>0.91</td>
<td>1.17 (0.61–2.34)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>1.18 (1.01–1.37)</td>
<td>0.024</td>
<td>–</td>
<td>–</td>
<td>1.05 (0.79–1.39)</td>
</tr>
</tbody>
</table>

HbA1c was not obtained in 50 patients (6.5%). Two models of multivariate analysis were used. In the first model, age, hypertension, dyslipidemia, diabetes mellitus, Killip class, hemoglobin, eGFR, creatinine, previous angina, previous PCI, primary PCI and use of aspirin and anti-hyperglycemic agent were adjusted. In the second model, HbA1c was added to these variables. Abbreviations as in Tables 1,2.

In-Hospital Mortality

Incidence of AKI has progressively declined (from 26.6% in the year 2000 to 19.7% in 2008). Therefore, CI-AKI seems not to be the main cause of AKI in patients with AMI, but diabetes mellitus and HbA1c were not (Table 3).

In the current study, the incidence of AKI was 13%, which is similar to these previous reports. In the last decade, primary PCI has become the treatment of choice for patients with AMI, and number of patients who receive coronary angiography has been rapidly increasing. The contrast medium is nephrotoxic, and may cause acute tubular necrosis. This is termed ‘contrast-induced AKI (CI-AKI)’.5,21–23

There is a concern about the risk of CI-AKI for patients undergoing coronary angiography and primary PCI for AMI. In the present study, however, both emergency angiography and primary PCI were not associated with AKI in AMI patients. In the ACTION registry, which enrolled 59,970 patients with AMI who were mostly treated with primary PCI, reported that 16.1% of patients developed AKI during hospitalization.21 In the current study, the incidence of AKI was 13%, which is similar to these previous reports.

The major findings of this study are: (1) AKI developed in 13% after AMI; (2) AKI was associated with in-hospital mortality after AMI; and (3) admission hyperglycemia was an independent risk factor for AKI in patients with AMI.

AKI and In-Hospital Mortality

In the current study, the in-hospital mortality of patients with AKI was 8-fold as high as those without AKI. It has been well demonstrated that AKI is a strong predictor of mortality after AMI. In the ACTION registry, the in-hospital mortality in-
increased as the stage of AKI advanced, and overall mortality in patients with AKI was 15%, which was 7.5-fold higher as compared to those without AKI (2%).

Comorbid factors and the severely ill condition of patients with AKI are at least in part responsible for the higher mortality of these patients. Even after adjusting these factors, however, AKI remains as an independent predictor of mortality in AMI patients. Previous studies have suggested that AKI can affect the heart through several pathways.24–26

**Predictors of AKI in AMI**

Worsening of renal function may have negative effects on heart and circulation, resulting in higher mortality after AMI in patients with AKI.27 In turn, a rapid worsening of cardiac function may lead to AKI. The concept of cardiorenal syndrome (CRS) has become widely accepted in recent years.17,28 The latter condition, characterized by initiation and/or progression of renal insufficiency secondary to heart failure, is the most common type of CRS, but its mechanisms are multiple and complex.

Acute decline in renal function is not simply due to decreased renal blood flow; acceleration in cardiovascular pathobiology through activation of inflammatory pathways is considerably responsible for the development of AKI. In patients with AMI, neurohormonal, immunological and inflammatory pathways are activated, resulting in kidney injury.29 Inflammatory biomarkers, including pentraxin 3, interleukin-1 and -6, tumor necrotic factor-α and so on, have been shown to be associated with AKI.29–31

Recently, several studies have focused on the importance of acute hyperglycemia as a determinant of outcome in patients with AMI. Elevation of PG on admission, acute hyperglycemia, is a common feature early after AMI, even in the absence of diabetes mellitus.8,13,15,12 Numerous studies have described the association between acute hyperglycemia and adverse outcome in patients with AMI. Multiple physiological studies have shown that hyperglycemia has a direct detrimental effect on ischemic myocardium through several mechanisms, including oxidative stress, inflammation, apoptosis, endothelial dysfunction, hypercoagulation, and platelet aggregation.14–16

Brief episodes of antecedent myocardial ischemia have protective effects against subsequent prolonged ischemia, termed ‘ischemic preconditioning’. Such effects are also generated by brief intermittent ischemia after the ischemic event (post-conditioning) and observed even in remote organs (remote conditioning). A recent study has reported that remote post-conditioning prevents the development of AKI after PCI.32 We have previously reported that admission hyperglycemia abolishes ischemic preconditioning.33,34 It may also attenuate renoprotective effects of ischemic preconditioning in patients with AMI.

Previous clinical studies have reported that elevated PG is associated with worsening of renal function after cardiac surgery or coronary angiography.21,23 In the current study, patients with elevated glucose on admission were at higher risk of death during hospitalization for AMI, regardless of the use of coronary angiography or primary PCI. Although it remains unknown whether hyperglycemia is causally related to deterioration of kidney function, the positive relationship between admission glucose and the development of AKI remained significant even after adjusting potential confounding factors, suggesting that hyperglycemia is not a simple surrogate marker of AKI.

**Study Limitations**

The present results should be interpreted in the context of several potential limitations. First, the present study was a single-center and retrospective study. We did not obtain sufficient data on contrast medium volume to analyze the relationship between volume of contrast medium and AKI. Second, the mechanisms by which acute hyperglycemia is correlated with AKI in AMI patients remained unclear. The relationship between acute hyperglycemia and systemic inflammatory responses, and the mechanisms of kidney injury following AMI should be analyzed in basic and clinical studies in the future.

**Conclusions**

Admission hyperglycemia could be an independent predictor for AKI in AMI patients. Careful monitoring of renal function should be done for patients with AMI and admission hyperglycemia.

**Disclosures**

There is no financial support for this study.

**References**


30. Anker SD, Coats AJ. How to RECOVER from RENAISSANCE? The significance of the results of RECOVER, RENAISSANCE, RENEWAL and ATTACH. Int J Cardiol 2002; 86: 123 – 130.


