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Acute hyperglycemia an independent risk factor for contrast-induced nephropathy in patients undergoing primary percutaneous coronary intervention for STEMI

Abstract

Background: Patients undergoing primary PCI are at high risk for contrast-induced nephropathy (CIN), a complication that has a serious impact on in-hospital outcome. Acute hyperglycemia is common in patients with STEMI even in the absence of history of DM and has been identified as a major predictor of in-hospital mortality and morbidity.

Objective: To determine the association between admission acute hyperglycemia and the risk of subsequent CIN in patients with STEMI undergoing primary PCI.

Patients and Methods: The study included 120 patients who presented with acute STEMI and were treated with primary PCI. The patients were divided into 2 groups:

Group A: Included (60) patients with acute hyperglycemia (blood glucose >198 mg/dl)

Group B: Included (60) patients without acute hyperglycemia on admission.

Serum creatinine was measured at the time of admission and daily for the following 5 days. CIN was defined as an increase of ≥25% or an absolute increase of ≥0.5 mg/dl in serum creatinine level

Results: There was a statistically significant difference regarding the incidence of CIN and need for dialysis between both groups, where CIN occurred in 23 (38.3%) patients, of which 9 patients required dialysis in group A, while in group B, CIN occurred in 8 (13.3%) patients, of which none needed dialysis ($P < 0.01$).

In-hospital adverse events occurred more frequently in group (A) than group (B). In Group (A) 9 patients (15%) had acute pulmonary oedema (APO), cardiogenic shock and needed mechanical ventilation. On the other hand in Group (B) 2 patients (3.3%) had APO and 1 patient (1.7%) had cardiogenic shock and required mechanical ventilation **(P< 0.05)** Overall in-hospital mortality of the study population was 10% (n = 6) all of which were in group (A) ($P < 0.05$).

Conclusion: In patients undergoing primary PCI, acute hyperglycemia is associated with increased incidence of CIN as well as increased incidence of in-hospital adverse events and in-hospital mortality.

Keywords: contrast-induced nephropathy, cin, acute hyperglycemia, primary pci, stemi

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Abbreviations: PCI, percutaneous coronary intervention; CIN, contrast-induced nephropathy; STEMI, ST-segment elevation myocardial infarction

Introduction

Patients undergoing primary percutaneous intervention (PCI) are at high risk for contrast-induced nephropathy (CIN), a complication that has a serious impact on in-hospital outcome and may affect the overall benefit of primary PCI. In-hospital mortality has been shown to be 20 times higher in patients who experience CIN after primary PCI.[1] Oxidant stress-mediated injury and renal medullary hypoxia and ischemia, due to endothelial dysfunction and vasoconstriction as well as enhanced apoptosis in response to contrast medium administration, have been implicated as causative factors for CIN.[2] All these processes are also activated in the setting of acute hyperglycemia and there is clear evidence that marked fluctuations in glucose levels have consequences that are even more deleterious than those of chronically elevated glucose.[3] Acute hyperglycemia (defined as glucose levels >198 mg/dL (11 mmol/L),[4] is common in patients with *STEMI*, even in the absence of history ofdiabetes mellitus (*DM*).[5] Increased glucose levels at hospital presentation has been identified as a major independent predictor of both in-hospital mortality and congestive heart failure in patients presenting with STEMI even in those without pre-existing DM.[6,7] The present study aimed at determining the association between acute hyperglycemia (regardless of pre-existing diabetic status) and the risk of subsequent development of CIN in patients presenting with STEMI treated by primary PCI.

Materials and methods

This study prospectively enrolled *120* patients who presented to the emergency department of the *National Heart Institute (NHI)* diagnosed with a first attack of acute *ST*-elevation myocardial infarction according to the universal definition of MI.[8] The study was approved by the Ethics committee of Ain Shams University. The objectives

of the project and study design were explained completely to the participants and informed consent was obtained from them as well as they were ensured their data would remain private.

The study included patients presenting within *12 hours* from the onset of symptoms (characteristic chest pain lasting for at least *30 minutes*, not responsive to nitrates, with electrocardiographic ST-segment elevation of at least *0.1 mv* in two or more contiguous leads, or new left bundle-branch block) and were treated with primary PCI in at timely fashion (door to balloon time < 90 minutes).

The patients were divided into 2 groups according to presence of acute hyperglycemia (blood glucose >198 mg/dl on admission):[4]

1. **Group A:** Which included (60) patients with acute hyperglycemia.
2. **Group B:** Which included (60) patients without acute hyperglycemia.

The following patients were excluded from the study: Patients with history of pre-existing renal diseases, those with baseline creatinine clearance ≤30 ml and patients on regular renal dialysis. Patients who underwent cardiac surgery for emergency coronary revascularization and/or mechanical complications or patients who died during PCI were also excluded from the study.

The patients were subjected to

A. Proper history taking and examination

All patients were subjected to thorough history taking, full clinical examination including general and local cardiac examination and 12 lead E.C.G.

B. Laboratory investigations

Admission serum glucose level was measured. Serum creatinine was measured at the time of admission (baseline venous sample of serum creatinine withdrawn prior to the primary PCI procedure) and every day of the following five days during hospital stay and the GFR was calculated by **cockcroft-Gault** formula.[9] Contrast-induced nephropathy was defined as impairment of renal function occurring within 48 hours after administration of contrast medium, manifested by an increase in serum creatinine level of 0.5 mg/dl or by a relative increase of 25% over the baseline value.[10]

C. Echocardiography

A standard trans-thoracic echocardiographic evaluation was performed to all patients after hospital admission with special emphasis on the left ventricular ejection fraction by modified Simpson's method.

D. Coronary angiography and 1ry PCI

All patients received chewable aspirin (300 mg) and clopidogrel (600 mg loading dose) before coronary angiography. Primary PCI was performed by a 24-hour on-call interventional team, according to standard clinical practice, including balloon angioplasty and/or stent implantation were performed only for IRA according to lesion anatomy, with successful mechanical restoration of antegrade flow and achieving the desired end results. After Primary PCI; IRA flow was graded according to the Thrombolysis in Myocardial Infarction (TIMI) flow classification (TIMI 0, 1, 2, 3)[11] and myocardial reperfusion was graded according to Myocardial Blush Grade (MBG) classification (MBG 0, 1, 2, 3)[12] The type of contrast used was Ioversol (Optiray 300)® which is a low osmolar non ionic contrast media and volume of contrast medium used in every procedure was reported. After angioplasty, all patients were admitted to the coronary care unit, where standard guideline directed medical treatment was continued.

During hospitalization the following adverse clinical events were reported:

i. Acute pulmonary edema and mechanical ventilation.

ii. Acute renal failure requiring emergency hemodialysis.

iii. Cardiogenic shock.

iv. Arrhythmias and death.

Statistical analysis

Data was analyzed using IBM SPSS v.21. Continuous variables were summarized in the form of mean ± SD. Categorical variables in the form of count and percentages. Statistical analysis tests include unpaired t-test for metric variables and Chi Square test for categorical ones. Logistic regression was used to assess the significance of individual variables while fixing for others. P- values <0.05 were considered significant.

Results

Baseline demographic, clinical, laboratory and echocardiographic data

Table 1 summarizes the baseline demographic, clinical, laboratory and Echocardiographic data of both studied groups (p value > 0.05). Age, weight and prevalence of DM were statistically higher in **group A** (p value= 0.016, 0.022 and 0.001 respectively), however there was no statistically significant difference between the two groups regarding rest of risk factors, baseline EF or baseline kidney function (p value > 0.05).

Table 1 Comparison between the two studied groups regarding the baseline characteristics

	Group A	Group B	P -value
Gender (Male/Females) n (%)	44(73%)/16(27%)	52(87%)/8(13%)	0.068
Age (Years)	57.10±10.2	51.97±12.6	0.016
Weight (Kg)	83.67±14.5	78.18±11.3	0.022
Smoking	40 (67%)	45 (75%)	0.315
HTN	27 (45%)	19 (32%)	0.133
DM	35 (58%)	17 (28%)	0.001
Dyslipidemia	34 (57%)	24 (40%)	0.068
History of IHD	21 (35%)	15 (25%)	0.319
LVEF %	48.52 ± 9.9	51.07 ± 8.3	0.131
Baseline creat (mg/dl)	0.98 ± 0.2	0.96 ± 0.2	0.651
Baseline eGFR (ml/min)	99.27 ± 32.2	103.30 ± 36.8	0.524

HTN, hypertension; DM, diabetes mellitus; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; Creat, creatinine; eGFR, estimated glomerular filtration rate

Procedural data

There was no statistically significant difference between the two studied groups regarding the type of infarction & infarct related artery (IRA), symptom to balloon time as well as the volume of contrast used (p value > 0.05). Although there was no statistically significant difference between the 2 studied groups regarding the final TIMI flow grade (p value = 0.174), however the MBG was statistically significantly lower in **group A** (p=0.025) (Table 2).

Table 2 Comparison between the two studied groups regarding the procedural data

		Group A (N=60)	Group B (N=60)	P -value
Type of STEMI	Anterior	38 (63.3%)	39 (65.0%)	0.841
	Global	2 (3.3%)	1 (1.7%)	
	Inferior	20 (33.3%)	20 (33.3%)	
Infarct artery	LAD	39 (65.0%)	41 (68.3%)	0.635
	LCX	7 (11.7%)	5 (8.3%)	
	OM	1 (1.7%)	0 (0.0%)	
	RCA	12 (20.0%)	13 (21.7%)	
	Ramus	0 (0.0%)	1 (1.7%)	
	Left main	1 (1.7%)	0 (0.0%)	
Symptom to balloon (hr)		6.97 ± 2.0	7.09 ± 3.0	0.797
TIMI flow		2.75 ± 0.4	2.85 ± 0.4	0.174
MBG		2.28 ± 0.6	2.52 ± 0.5	0.025
contrast volume (ml)		215.42 ± 50.3	219.08 ± 47.8	0.683

STEMI, ST-elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction; MBG, myocardial blush grade; LAD, left anterior descending; LCX, left circumflex; OM, obtuse marginal; RCA, right coronary artery

Renal functions and incidence of CIN

There was no statistically significant difference between the two studied groups regarding the baseline serum creatinine level & estimated GFR on admission (p value > 0.05). However there was a statistically highly significant difference between the two groups regarding the maximum recorded creatinine during hospital stay, being higher in group A (1.5+0.9mg/dl in group A vs 1.1+0.2 mg/dl in group B) (p = 0.001) (Table 3 & Figure 1).

Table 3 Comparison between the two studied groups regarding the baseline renal functions, incidence of CIN & need for dialysis

	Group A		Group B		P-Value
	Mean	SD	Mean	SD	
Baseline creat (mg/dl)	0.98	0.2	0.96	0.2	0.651
Baseline eGFR (ml/min)	99.27	32.21	103.3	36.79	0.524
Max. creat (mg/dl)	1.53	0.87	1.11	0.24	0.001
eGFR at max.creat (ml/min)	74.53	34.86	90.48	31.43	0.01
Time to max. creat (day)	3.78	0.8	3.5	0.53	0.36
CIN	23	38.30%	8	13.30%	0.002
Dialysis	9	15.00%	0	0.00%	0.002

Creat, creatinine; eGFR, estimated glomerular filtration rate; CIN, contrast induced nephropathy

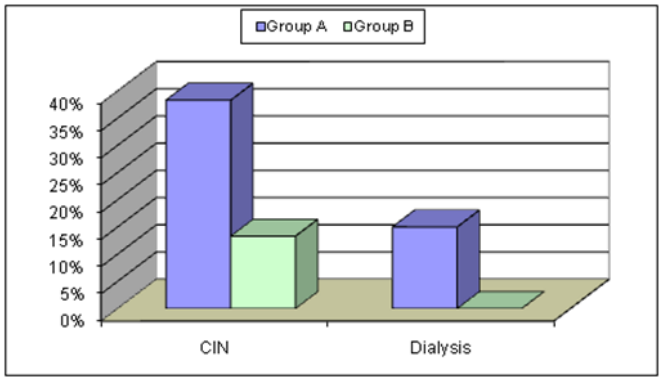

Figure 1 Comparison between the two studied groups regarding incidence of CIN & need for dialysis.

There was also a statistically significant difference between the two groups regarding the estimated GFR of maximum creatinine during hospital stay, (74.5+34.9 ml/min in group A vs 90.5+31.4ml/min in group B) (p<0.05). The timing of peak creatinine during hospital stay was nearly equal in both groups with no statistically significant difference (3.8+0.8 day in group A vs 3.5+0.5 day in group B) (p> 0.05). There was a highly statistically significance difference regarding the incidence of CIN and need for dialysis between both studied groups, where CIN occurred in 23 (38.3%) patients, of which 9 patients required dialysis in group A, while in group B, CIN occurred in 8 (13.3%) patients, none of which needed dialysis (p < 0.01).

In-hospital complications and mortality

In-hospital adverse events occurred more frequently in the group (A) than in group B (Table 4). The incidence of Ventricular tachycardia/ventricular fibrillation (VT/VF), Acute pulmonary oedema (APO) cardiogenic shock & need for mechanical ventilation were significantly higher in group (A) (p < 0.05). Overall in-hospital mortality of the study population was 10% (n = 6) in group (A), while in group (B) no mortality was recorded (p value = 0.013). Logistic regression was used to assess the relationship between CIN and each of acute hyperglycemia, age, weight and diabetic status. The odds of having CIN was 3.85 times more for patients presenting with acute hyperglycaemia than in the control group (p: 0.007, OR 95%CI: 1.45-10) while adjusting for all other variables. For age, the odds of having CIN were 1.05 times more for each one-year increase in age. (p: 0.034, OR 95%CI: 1.003-1.01). The other two variables (weight and diabetic status) were non-significant as shown in Table 5.

Table 4 Comparison between the two studied groups regarding in-hospital morbidity and mortality

	Group A (n=60)		Group B (n=60)		P-value
	No.	%	No.	%	
VT/VF	9	15%	2	3.30%	0.027
APO	9	15%	2	3.30%	0.027
Cardio shock	9	15%	1	1.70%	0.008
Mech.Vent.	9	15%	1	1.70%	0.008
Mortality	6	10.00%	0	0.00%	0.013

VT/VF, ventricular tachycardia/ventricular fibrillation; APO, acute pulmonary oedema; Mech.Vent, mechanical ventilation

Table 5 Logistic regression to assess the relationship between CIN and each of individual risk factors (acute hyperglycemia, age, weight and presence of diabetes)

Variable	p-value	Odds Ratio	95%CI for Odds Ratio
Acute Hyperglyecmia	0.007**	3.85	1.45 - 10
Age	0.034*	1.05	1.003 – 1.1
Weight	0.49	0.99	0.95 – 1.02
DM	0.91	1.05	0.41 – 2.70

**highly significant, *significant

Discussion

In the present study, the presence of acute hyperglycemia in STEMI patients undergoing primary PCI, was associated with a significant increase in incidence of CIN and need for dialysis. The association between high glucose levels and acute kidney injury is supported by previous studies.[13-15] Marinzi et al.[16] in 2010showed that in STEMI patients treated with primary PCI, acute hyperglycemia was an independent predictor of CIN, where patients with acute hyperglycemia had a 2-fold higher incidence of CIN than those

without acute hyperglycemia (p<0.001) (27% vs 12%, P < 0.001). Contrast induced nephropathy requiring hemofiltration was also significantly higher in patients with acute hyperglycemia (6% vs 2% p = 0.005).[16]

In the present study, hyperglycemia associated increased CIN risk and need for dialysis occurred regardless of the Diabetic state. Surprisingly, Diabetes mellitus itself was not a statistically significant risk factor for CIN. Similar results were reported by Marenzi et al.[16] who found that CIN rate among patients with acute hyperglycemia, was higher in nondiabetic than in diabetic patients (38% vs 16%, P =.003).[16] Shacham et al.[17] in 2015 also found that admission hyperglycemia was an independent risk factor for the development of acute kidney injury (AKI) among nondiabetic STEMI patients undergoing primary PCI. He studied 1,065 nondiabetic STEMI patients undergoing primary PCI. Patients were stratified according to admission glucose levels into normal (<140 mg/dl), mild (140–200 mg/dl), and severe (>200 mg/dl) hyperglycemia groups. Patients with severe admission hyperglycemia had a significantly higher rate of acute kidney injury (AKI) compared to patients with no or mild hyperglycemia (20 vs. 7 and 8%, respectively; p = 0.001) and had a significantly greater serum creatinine change during hospitalization (0.17 vs. 0.09 and 0.07 mg/dl, respectively; p = 0.04). In multivariate logistic regression, severe hyperglycemia was shown to be an independent predictor of AKI (OR = 2.46, 95% CI 1.16–5.28; p = 0.018).[17] Among patients with no prior history of DM, hyperglycemia may reflect previously undiagnosed diabetes, pre-existing carbohydrate intolerance, stress-related glucose intolerance, or a combination of these factors.[6] Stress is accompanied by high levels of catecholamines such as adrenaline and cortisol. These hormones increase glycogenolysis and lipolysis and reduce insulin sensitivity, resulting in elevated glucose levels.[18]

Several effects of acute hyperglycemia have direct negative impact on renal function and increase renal toxicity of contrast agents. Hyperglycemia, even in absence of diabetes, leads to increased endothelin and angiotensin levels, causing intrarenal vasoconstriction increasing the medullary lactate level, reducing pH and oxygen delivery and increasing reactive oxygen species and oxidative stress.[19,20] Thus, acute hyperglycemia may exacerbate the deleterious effects of contrast agents on the kidney. Moreover, acute hyperglycemia may induce osmotic diuresis, resulting in volume depletion and dehydration and further increasing *CIN* risk and severity.

In the present study acute hyperglycemia was associated with statistically significant lower MBG after 1ry PCI as compared to patients without acute hyperglycemia. Acute hyperglycemia was also associated with statistically significant higher in-hospital adverse events (VT/VF, APO, cardiogenic shock and need for mechanical ventilation) and in-hospital mortality. Acute hyperglycemia is associated with several adverse effects that contribute to poor outcome in STEMI. They include increased oxidative stress, increased cytokine activation, Inflammatory response, endothelial dysfunction and impaired microcirculatory function as manifested by post-PCI no-reflow and impaired ischemic preconditioning.[4,21-25] Hyperglycemia has also been shown to have several prothrombotic effects and enhanced platelet activation with subsequent increased risk for thrombotic events.[26-29]

Several studies have demonstrated that acute hyperglycemia is a powerful predictor of mortality, larger infarct size and increased risk of cardiovascular complications in myocardial infarction patients regardless of the diabetic state.[30-35] For every 18-mg/dL increase in glucose level, there is a 4% increase in mortality in nondiabetic patients presenting with myocardial infarction.[36] Several studies showed that hyperglycemia during acute illness is associated with greater mortality in non diabetic patients than in those with documented diabetes.[6,37-41] This might be explained by the fact that diabetic patients may have had more opportunity to adapt to a hyperglycemic milieu and therefore are less immediately affected by acute hyperglycemia than patients who are naive to elevated glucose levels. Another possibility is that hyperglycemia is marker for illness severity. Also, individuals described as non-diabetic may actually have undiagnosed diabetes that when untreated predisposes to worse outcomes.[42]

Study limitations

This is a single centre study which included a relatively small number of patients. The present study did not include HBA1c evaluation which could have provided data to compare the effect of acute vs chronic hyperglycemia. Finally, being a short term study, no long term data regarding renal functions, cardiovascular complications or long term mortality could be provided, however this could be a subject for future studies.

Conclusion

In the present study, acute hyperglycemia, was associated with increased incidence of CIN in STEMI patients undergoing primary PCI independent of the diabetic status of the patients. Acute hyperglycemia was also associated with increased incidence of in-hospital adverse events and in-hospital mortality.

Recommendation

Since admission glucose level measurement is readily available for all patients presenting with STEMI, this variable could be incorporated into risk calculation models for identification of patients at risk for development of CIN after primary PCI.

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None.

Conflicts of interest

No financial interest or any conflict of interest exists.

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