

# Impact of uncontrolled glycosylated hemoglobin on contrast-induced acute kidney injury in patients with type 2 diabetes mellitus undergoing percutaneous coronary intervention

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## Abstract

**Introduction:** Numerous studies revealed that hyperglycemia in patients undergoing percutaneous coronary intervention (PCI) increases the risk of acute kidney injury (AKI) in hospital admission individuals. However, there is a little data regarding the effect of long-standing hyperglycemia on the presence of AKI in patients with myocardial infarction undergoing primary PCI.

**Objectives:** In this study, we investigated the effect of chronic poor glycemic control (using HbA<sub>1c</sub>, as an index of glucose control in the last 2-3 months) on AKI occurrence in individuals with type 2 diabetes mellitus (T2DM) and ST-elevation myocardial infarction (STEMI) undergoing coronary angiography and primary PCI.

**Patients and Methods:** We prospectively studied 120 patients with T2DM and STEMI undergoing primary PCI. According to glycosylated hemoglobin (HbA<sub>1c</sub>), individuals were divided into two groups, patients with HbA<sub>1c</sub> <7% (group 1, n = 47) and patients with HbA<sub>1c</sub> ≥ 7% (group 2, n = 73). Medical records of both groups were reviewed for the occurrence of AKI.

**Results:** AKI was found in 3 of 47 patients (6.38%) in group 1 and in 16 of 73 patients (21.9%) in group 2 ( $P=0.043$ ). There was no statistically difference in baseline serum creatinine and estimated glomerular filtration rate between the two groups. Group 2 had significantly higher HbA<sub>1c</sub> ( $8.6 \pm 1.6$  vs.  $5.8 \pm 1.2$  %;  $P=0.001$ ) and higher admission glucose levels ( $259 \pm 95$  mg/dL vs.  $163 \pm 71$  mg/dL;  $P=0.001$ )

**Conclusion:** Elevated HbA<sub>1c</sub> was associated with higher risk of AKI in T2DM with STEMI who treated with primary PCI.

## Introduction

Coronary artery disease (CAD) is one of the leading causes of death worldwide and remains a substantial contributor to morbidity, mortality and healthcare expenditure. The treatment of choice for many individuals with stable CAD is revascularization using percutaneous coronary intervention (PCI). Advances in PCI technology have been led to increasing proportion of individuals undergoing coronary revascularization by this approach. In Europe, 15 million people had PCI in 2010, and it is estimated that 15 million individuals undergo PCI in the United States each year (1).

Contrast-induced acute kidney injury (CI-AKI) continues to be one of the most common major adverse side effect of cardiac catheterization, and is associated with short- and long-term morbidity and mortality (2,3). This is particularly true in the population presenting with acute ST-

## Core tip

In a study on 120 patients with type 2 DM (T2DM), we found, elevated HbA<sub>1c</sub> was associated with higher risk of acute renal failure in type 2 diabetics with ST-elevation myocardial infarction who treated with primary percutaneous coronary intervention.

elevation myocardial infarction (STEMI). There is an increased incidence of AKI in patients undergoing coronary angiography (CAG) and PCI (4,5) mainly due to high dosage of the contrast used, advanced age, advanced vascular disease, hypertension, and diabetes mellitus (DM) (6).

The increased prevalence of type 2 DM (T2DM), as a known significant risk factor of CI-AKI, also contributes to this process. A long-standing hyperglycemic milieu is considered to be responsible for the increased incidence of CI-AKI in patients with T2DM (7). Several studies have reported that acute hyperglycemia also increases the risk of CI-AKI and therefore mortality (8-10). This

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entity has been associated with the pathophysiological similarity of the adverse effects of both hyperglycemia and iodinated contrast media (CM) on kidneys (oxidative stress, endothelial dysfunction and vasoconstriction) (11-13). However, there are no adequate clinical studies to demonstrate whether long-standing poor glycemic control further increases the risk of CI-AKI.

## Objectives

In this study, we investigated the effect of chronic poor glycemic control (using HbA<sub>1c</sub>, as an index of glucose control in the last 2-3 months) on AKI occurrence in patients with T2DM and STEMI undergoing coronary angiography and primary PCI.

## Patients and Methods

### Study population

This study was a prospective investigation conducted on 120 patients with T2DM admitted during the period from January 2013 to January 2016 at National Heart Institute and Theodo Bilhaz Institute, Cairo, Egypt, with acute STEMI for coronary angiography and treated by PCI. DM was diagnosed by laboratory examination, previous history of this disease and history of receiving antidiabetic drugs. STEMI was diagnosed as patients had typical chest pain, serial elevation of cardiac troponin with echo-heart changes. Primary PCI was performed on patients with symptoms from 12 to 24-hour duration. Contrast media (CM) used in procedures was iodixanol (Visipaque, GE healthcare, Ireland) or iohexol (Omnipaque, GE healthcare, Ireland). Following CAG and PCI procedures, normal saline (0.9%) was given intravenously at a rate of 1 mL/kg/h for 24 hours after contrast exposure. The hydration rate was lessened in individuals with volume overload as also in subjects with heart failure. Left ventricular ejection fraction (LVEF) was evaluated in all participants within the first 48 hours of admission. Patients with estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m<sup>2</sup> and critically all patients having mechanical ventilation or intra-aortic balloon counter-pulsation were excluded from the study.

According to glycosylated hemoglobin (HbA<sub>1c</sub>), patients were divided into two groups, patients with HbA<sub>1c</sub> <7% (group 1, n = 47) and patients with HbA<sub>1c</sub> ≥7% (group 2, n = 73). A cut off point of 7% was chosen because it is the recommended target of glycemic control for T2DM to reduce complications (14).

Random blood glucose level was measured on admission. HbA<sub>1c</sub> levels were measured from blood samples taken within 24 hours of hospital admission. Renal function tests (serum creatinine, blood urea, serum potassium, serum sodium, and serum uric acid) were measured on hospital admission, and at least once a daily. The eGFR was calculated using the abbreviated modification of diet in renal disease equation (MDRD) (15). Baseline renal insufficiency was categorized as admission eGFR of <60 mL/min/1.73 m<sup>2</sup> (16). AKI was determined using KDIGO guidelines (17) and defined as increase in serum creatinine

by 0.3 mg/dL within 48 hours of admission.

### Ethical issues

1) The research followed the tenets of the Declaration of Helsinki and its later amendments; 2) informed consent was obtained; and 3) This study was approved by the Ethics Committee of Theodor Bilharz Research Institute, Cairo, Egypt.

### Statistical analysis

All data were presented as mean ± standard deviation (SD) or percentages. Continuous variables were compared using the unpaired two-tailed Student's *t* test (using GraphPad QuickCalcs software). The *P* values for the categorical variables were calculated with the chi-square test. Pearson's rank correlation test was used to analyze the correlation between HbA<sub>1c</sub> and serum creatinine (using MedCalc software). Multi-variate linear regression analysis was used to study the predictive factors of CI-AKI. Statistical analysis was performed using SPSS version 16 for Windows software (SPSS Inc., Chicago, IL, USA). A *P* value <0.05 was considered statistically significant and *P* value <0.01 was considered highly statistically significant.

## Results

The patients included in this study were 120 patients with T2DM with mean age 62.7 ± 9.2 years (75% males). Around 47 of whom (39.2%) had HbA<sub>1c</sub> <7% and 73 of whom (60.8%) had HbA<sub>1c</sub> level ≥7%. The baseline demographic, clinical and laboratory characteristics of patients according to the HbA<sub>1c</sub> levels are presented in Table 1. The two groups were comparable regarding age, gender, hypertension, dyslipidemia, hyperuricemia and extent of coronary artery disease.

Patients with HbA<sub>1c</sub> level ≥7% were more likely to be treated with insulin (58.9% vs. 17.02%; *P* < 0.001) with significantly higher admission glucose levels (259 ± 95 vs. 163 ± 71 mg/dL; *P* = 0.001), and higher HbA<sub>1c</sub> (8.6 ± 1.6 vs. 5.8 ± 1.2; *P* = 0.001)

Table 2 compares the serum creatinine changes, intravenous contrast volume applied and the occurrence of AKI according to HbA<sub>1c</sub> levels. There was no statistically difference in baseline serum creatinine and eGFR between the two groups. The total volume of CM was not statistically different between the two groups. Serum creatinine change at 48 hours after PCI and on discharge was highly significant in group 2 with HbA<sub>1c</sub> ≥7% than group 1 with HbA<sub>1c</sub> <7%. AKI was found in 16 of 73 (21.9%) in group 2 of patients with HbA<sub>1c</sub> ≥7% and in 3 of 47 (6.38%) in group 1 of patients with HbA<sub>1c</sub> <7% (*P* = 0.0436).

There was a positive significant association between the HbA<sub>1c</sub> level and the incidence of AKI in the studied patients (Figure 1).

Multi-variate linear regression analysis was applied to define independent risk factors of AKI. According to regression analysis, HbA<sub>1c</sub>, age, LVEF and volume of CM were found to be independent risk factors of AKI (Table 3). After adjusting for age, sex, LVEF, multi-vessel disease,

**Table 1.** Demographic, clinical and laboratory characteristics of studied patients

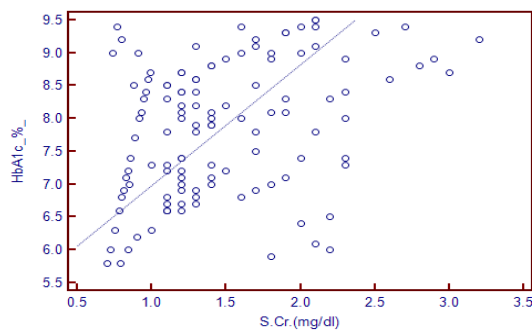
Variables	Group 1 (HbA <sub>1c</sub> <7%) n = 47	Group 2 (HbA <sub>1c</sub> ≥7%) n = 73	P value
Age (y)	59.4 ± 9.3	60.3 ± 8.4	0.5839
Gender (M/F)	34/13 (72.3%/27.7%)	56/17 (76.7%/23.3)	0.7434
Systolic BP (mm Hg)	132.8 ± 23.5	138.3 ± 28.2	0.2688
Diastolic BP (mm Hg)	89.2 ± 16.6	92.6 ± 21.5	0.3588
Insulin therapy	8 (17.02%)	43 (58.9%)	0.0001
Glucose level at admission (mg/dL)	117.6 ± 36.4	238.3 ± 48.2	0.0001
HbA <sub>1c</sub> (%)	5.8 ± 1.2	8.6 ± 1.6	0.0001
Total cholesterol (mg/dL)	170.4 ± 36.7	171.8 ± 38.2	0.8426
Triglycerides (mg/dL)	86.3 ± 18.4	88.4 ± 19.2	0.5534
Serum uric acid (mg/dL)	6.43 ± 3.21	6.64 ± 2.52	0.6901
Personal history of MI	8 (17.02%)	19 (26.03%)	0.3525
Family history of CAD	14 (29.8%)	29 (39.7%)	0.3633
No. of stenosed coronary arteries			
1	11 (23.4%)	15 (20.5%)	0.8812
2	16 (34.04%)	21 (28.8%)	0.6895
3	20 (42.6%)	37 (50.7%)	0.4965
Time to reperfusion (h)	7.3 ± 5.2	8.2 ± 4.9	0.3396
CRP (mg/L)	15.2 ± 6.3	16.7 ± 6.8	0.2274
CPK (units/L)	1368.4 ± 432.6	1412.8 ± 471.4	0.6041
LVEF (%)	51.3 ± 7.4	48.6 ± 8.2	0.0701

Abbreviations: BP, blood pressure; HbA<sub>1c</sub>, glycosylated hemoglobin; MI, myocardial infarction; CAD, coronary artery disease; CRP, C-reactive protein; CPK, creatinine phosphokinase; LVEF, left ventricular ejection fraction.

**Table 2.** Serum creatinine changes, intravenous contrast volume applied and the occurrence of AKI according to HbA<sub>1c</sub> levels

Variables	Group 1 (HbA <sub>1c</sub> <7%), n = 47	Group 2 (HbA <sub>1c</sub> ≥7%), n = 73	P value
Serum creatinine at admission (mg/dL)	1.24 ± 0.62	1.38 ± 0.64	0.2388
eGFR (mL/min/1.73 m <sup>2</sup> )	77.12 ± 16.7	74.23 ± 14.2	0.3121
Contrast volume (mL)	140.8 ± 12.4	138.7 ± 14.2	0.4081
Serum creatinine 48 h after PCI	1.31 ± 0.83	1.68 ± 0.62	0.0062
Serum creatinine at discharge	1.23 ± 0.65	1.43 ± 0.41	0.0408
AKI	3 (6.38%)	16 (21.9%)	0.0436

Abbreviations: eGFR, estimated glomerular filtration rate; PCI, percutaneous coronary intervention; AKI, acute kidney injury



**Figure 1.** Correlation between HbA<sub>1c</sub>% and serum creatinine (sCr) (r = 0.353, 95% confidence interval for r 0.186 to 0.501, P = 0.001)

volume of CM, and blood glucose, HbA<sub>1c</sub> remained an independent risk factor for CI-AKI.

**Discussion**

CI-AKI is a prevalent but underdiagnosed complication of PCI that is associated with increased in-hospital morbidity and mortality (18-21). The importance of this complication is being increasingly recognized. Several

**Table 3.** Multi-variate regression analysis of the risk factors for CI-AKI

Variables	β	P value
HbA <sub>1c</sub>	0.62	0.021
LVEF	- 0.37	0.041
Age	0.53	0.024
Contrast volume	0.59	0.022
Blood glucose	0.42	0.032

recent North American and European epidemiological studies have shown that the incidence of AKI is increasing at an alarming rate (22). Patients with diabetes mellitus, pre-existing renal insufficiency, congestive cardiac failure or advanced age are particularly susceptible to developing CI-AKI post-PCI.

The present investigation showed that, raised HbA<sub>1c</sub> level was correlated with increased incidence of CI-AKI in patients with T2DM (patients with an eGFR of ≥60 mL/min/1.73 m<sup>2</sup>) and STEMI undergoing PCI.

Several reports demonstrated that acute hyperglycemia was correlated with a significant increase of acute renal failure following primary PCI (23,24). Likewise, studies revealed that admission hyperglycemia in patients with

STEMI increased the incidence of acute renal failure, cardiac failure and mortality even in the absence of a history of T2DM (25-28).

The results of two recent studies regarding the relationship of hyperglycemia at admission and CI-AKI are particularly interesting. These studies have demonstrated similar rates of CI-AKI development in T2DM individuals with and without hyperglycemia at the time of admission (8,9). However, the development of CI-AKI was more common in non-diabetic patients compared to those without hyperglycemia at the time of admission. The difference might possibly be explained by the administration of a more aggressive insulin therapy in patients with T2DM during hospitalization. Additionally, a better hydration of these patients, since T2DM is recognized to be a risk factor for CI-AKI.

Individuals with DM have a high risk of developing CI-AKI and the incidence of AKI in diabetic subjects varies from 5.7% to 29.4%. The administration of radiocontrast media to diabetic patients reduces kidney parenchymal oxygenation (29). Exposure of diabetic patients to iodinated radiocontrast will lead to overproduction of endothelin. This could describe the boosted susceptibility of diabetic subjects to contrast agents (29).

The strengthened incidence of acute renal failure in diabetic subjects has also been contributed to hypersensitivity of kidney vascular elements of diabetics to adenosine, as a vasoconstrictive substance. In fact, experimental investigations detected heightened adenosine-induced vasoconstriction in renal tissues of diabetic animals while the use of adenosine receptor antagonists diminished the risk of extension of contrast nephropathy in both diabetic and also nondiabetic subjects (30,31). Moreover, hyperglycemia might cause hypovolemia by increasing the osmotic diuresis.

To date, there have been few studies on the relationship between long-standing poor glycemic control and CI-AKI. In their retrospective study, Ding et al (32) reported higher glycosylated albumin and HbA<sub>1c</sub> levels in patients with CI-AKI compared to those without CI-AKI (8.3 ± 1.6% vs. 7.5 ± 1.2% for HbA<sub>1c</sub>, respectively,  $P < 0.001$ ). However, in their study, it might be incorrect to suggest uncontrolled glucose levels as the primary cause of CI-AKI. In our study, eGFR, age, LVEF, and CM volume were comparable between the two groups. In other study, Yoshikawa et al (33) reported a 5% increase in serum creatinine and a decrease of 4 mL/min/1.73 m<sup>2</sup> in eGFR in patients with an HbA<sub>1c</sub> of ≥6.5% compared to those with an HbA<sub>1c</sub> of <6.5% following coronary computed tomography angiography ( $P < 0.001$ ). However, such a small change in the values neither fits the definition of CI-AKI nor has any known clinical implications. A recent report by Akyuz et al demonstrated no difference in the rate of AKI following elective PCI in type 2 diabetic patients undergoing elective PCI (34). Marenzi et al demonstrated similar rates of AKI development following primary PCI in T2DM patients with and without admission hyperglycemia (23).

The results of the present study might be explained

with the long and more marked effect of chronic intrarenal mechanisms on kidneys due to long standing poor glycemic control (i.e., changes in the intra-glomerular hemodynamics adjusted partially via local activation of the renin-angiotensin system, biochemical derangements, proteinuria, and hypoxia) in addition to the direct effect of hyperglycemia in terms of the development of CI-AKI in T2DM (35).

## Conclusion

In conclusion, an elevated HbA<sub>1c</sub> level is associated with a higher incidence of CI-AKI compared with an optimal HbA<sub>1c</sub> level in patients with T2DM (patients with an eGFR of ≥60 mL/min/1.73 m<sup>2</sup>) undergoing CAG and/or PCI.

## Limitations of the study

Our study has several limitations; 1) limited proportion of patients; 2) patients with acute STEMI could not receive good hydration before intervention, interpretation of the results to these patients might not be appropriate; 3) renal atheroembolism could not be completely excluded as the potential cause of AKI, although its risk was low at 48 hours; 4) these results might not be valid for patients with type 1 DM.

## Authors' contribution

AE and AA conceived the study and contributed reagents and tools. AMA and AA performed the experiments. AE analyzed the data and drafted the final manuscript; all authors read, revised, and approved the final manuscript.

## Conflicts of interest

There were no points of conflicts.

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