**Impact of Long-Standing Poor Glycemic Control on the Occurrence of Contrast-Induced Acute Kidney Injury in Patients with Type-II Diabetes Mellitus Undergoing Percutaneous Coronary Intervention**

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**Background:** Many studies revealed that hyperglycemia on hospital admission increase the risk of Acute Kidney Injury (AKI) in patients undergoing Percutaneous Coronary Intervention (PCI), however, there is a little data regarding the effect of long-standing hyperglycemia on AKI occurrence in patients with myocardial infarction undergoing primary PCI.

**Objectives:** The aim of this study was to evaluate the effect of long-standing poor glycemic control on AKI occurrence in patients with Type-II Diabetes Mellitus (T2DM) and acute ST-Elevation Myocardial Infarction (STEMI) undergoing primary PCI.

**Patients and Methods:** We prospectively studied 120 patients with T2DM and acute STEMI undergoing primary PCI. According to glycosylated hemoglobin (HbA1c), patients were divided into 2 groups, patients with HbA1c <7% (Group 1, n=47) and patients with HbA1c ≥ 7% (Group-II, n=73). The estimated Glomerular Filtration Rate (eGFR) was estimated using the abbreviated Modification of Diet in Renal Disease equation (MDRD) and patients with eGFR <60 ml/min/1.73 m² were excluded from the study. Medical records of both groups of patients were reviewed for the occurrence of AKI. AKI was determined using Kidney Disease/Improving Global Outcomes (KDIGO) guidelines and defined as increase in serum creatinine by 0.3 mg/dl (26.5 umol/l) within 48 hours of admission.

**Results:** AKI was found in 3 of 47 patients (6.38%) in Group-I and in 16 of 73 patients (21.9%) in Group-II (p = 0.0436). Baseline serum creatinine and estimated Glomerular filtration rate were comparable between the two groups. There was positive significant correlation between the HbA1c levels and the incidence of AKI in the studied patients (p=0.0001). Using multivariate regression analysis, HbA1c was found to be one of the independent risk factors of Contrast-Induced Acute Kidney Injury (CI-AKI).

**Conclusion:** An elevated HbA1c levels were associated with a higher incidence of CI-AKI compared with an optimal HbA1c levels in T2DM patients with an eGFR of ≥60 ml/min/1.73 m² and STEMI treated with primary PCI.

**Introduction**

Coronary heart disease 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 patients with stable Coronary Artery Disease (CAD) is revascularization using Percutaneous Coronary Intervention (PCI). Advances in PCI technology have resulted in increasing numbers of patients undergoing coronary revascularization via this approach. In Europe, 15 million people had PCI in 2010, and it is estimated that 15 million patients undergo PCI in the United States every 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-Elevation Myocardial Infarction (STEMI). Coronary Angiography (CAG) and PCI are associated with the highest rates of Acute Kidney Injury (AKI) [4,5] mainly related to the intra-arterial injection and to the high dosage of the contrast necessary, and also to the type of patients who have advanced age, one or more comorbid conditions, and more advanced vascular disease, hypertension, and Diabetes Mellitus (DM) [6].
The increased prevalence of Type-II Diabetes Mellitus (T2DM), 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 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].

**Objectives**

Since there are no adequate clinical studies to demonstrate whether long-standing poor glycemic control further increases the risk of CI-AKI. Accordingly, in this study, we investigated the effect of long-standing poor glycemic control (using HbA1c, as a marker of glucose control in the last 2-3 months) on AKI occurrence in patients with T2DM and STEMI undergoing CAG and primary PCI.

**Patients and Methods**

**Study population**

This a prospective study conducted on 120 patients with T2DM admitted during the period from January 2013 to May 2016 at National Heart Institute and Theodor Bilharz Research Institute, Cairo, Egypt, with acute STEMI for CAG and treated by PCI. DM was diagnosed by history of DM diagnosed previously or history of receiving anti-diabetic medications. 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 h duration. CM used in procedures was ioxidanol (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 24h after contrast exposure. The hydration rate was reduced in patients with volume overload as patients with heart failure. Left Ventricular Ejection Fraction (LVEF) was assessed in all patients within the first 48h of admission. Patients with Estimated Glomerular Filtration Rate (eGFR)<60ml/min/1.73m² and critically ill patients on mechanical ventilation or intra-aortic balloon counter pulsation were excluded from the study.

According to glycosylated hemoglobin (HbA1c), patients were divided into 2 groups, patients with HbA1c <7% (Group-I, n=47) and patients with HbA1c ≥7% (Group-II, n=73). A cutoff point of 7% was chosen because it is the recommended target of glycaemic control for T2DM to reduce complications [14].

Random blood glucose level was measured on admission. HbA1c levels were measured from blood samples taken within 24h 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 day. The eGFR was estimated using the abbreviated Modification of Diet in Renal Disease equation (MDRD) [15]. Baseline renal insufficiency was categorized as admission eGFR of <60ml/min/1.73m² [16]. AKI was determined using KDIGO guidelines and defined as increase in serum creatinine by 0.3 mg/dl (26.5umol/l) within 48 hours of admission [17].

**Ethical issues**

1) The research followed the tenets of the Declaration of Helsinki;
2) Informed consent was obtained from all patients included in the study and they were free to leave the study at any time; and 3) The research was approved by ethical committee of National Heart Institute and Theodor Bilharz Research Institute.

**Statistical analysis**

All data are presented as Mean±Standard Deviations (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 analyse the correlation between HbA1c and serum creatinine (using MedCalc software). Multivariate linear regression analysis was used to study the predictive factors of CI-AKI. Statistical analyses were 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 (75% males), 47 of whom (39.2%) had HbA1c <7% and 73 of whom (60.8%) had HbA1C level ≥7%. The baseline demographic, clinical and laboratory characteristics of patients according to the HbA1c levels are presented in (Table 1). The two groups were comparable regarding age, gender, hypertension, dyslipidemia, hyperuricemia and extent of coronary artery disease.

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

| Variables                     | Group-I (HbA1c <7%) No.47 | Group-II (HbA1c ≥7%) No.73 | P value |
|-------------------------------|---------------------------|---------------------------|---------|
| Age (years)                   | 59.4±9.3                  | 60.3±8.4                  | 0.5839  |
| Gender (MF)                   | 34/13(72.3%(/27.7%)      | 56/17(76.7%(/23.3%)     | 0.7434  |
| Systolic BLP (mm/Hg)          | 132.8±23.5                | 133.8±22.8                | 0.6888  |
| Diastolic BLP (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    | 117.6±38.4                | 238.3±48.2                | 0.0001  |
| HbA1c (%)                    | 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%)                 | 26(36.5%)                 | 0.3525  |
| Family history of CAD         | 14(29.8%)                 | 28(39.7%)                 | 0.3633  |

**No of stenosed coronary arteries**

| 1                              | 11(23.4%)                 | 15(20.5%)                 | 0.8495  |
| 2                              | 16(34.0%)                 | 21(28.8%)                 | 0.4965  |
| 3                              | 20(42.6%)                 | 37(50.7%)                 | 0.8985  |
| Time to reperfusion (h)        | 7.1±5.2                   | 8.2±4.9                   | 0.3396  |
| C-RP (mg/l)                    | 15.2±6.3                  | 16.7±6.8                  | 0.2274  |
| C-PK (units/l)                 | 1368.4±32.6               | 1412.8±47.4               | 0.6041  |
| LVEF (%)                       | 51.3±7.4                  | 48.6±8.2                  | 0.0701  |

BLP: Blood Pressure; HbA1c: Glycosylated Hemoglobin; MI: Myocardial Infarction; CAD: Coronary Artery Disease; C-RP: C - reactive protein; C-PK: Creatine Phosphokinase; LVEF: Left Ventricular Ejection Fraction;

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Patients with HbA1c 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 =0.0001), and higher HbA1c (8.6±1.6 vs 5.8±1.2; p=0.0001).

(Table 2) compares the serum creatinine changes, intravenous contrast volume applied and the occurrence of AKI according to HbA1c levels. Baseline serum creatinine and eGFR were comparable between the two groups. The total volume of CM was not statistically different between the two groups. Serum creatinine change at 48h after PCI and on discharge was highly significant in Group-II with HbA1c ≥7% than Group-I with HbA1c <7%. AKI was found in 16 of 73 (21.9%) in Group-II of patients with HbA1c ≥7% and in 3 of 47 (6.38%) in Group-I of patients with HbA1c <7% (p = 0.0436).

There was positive significant correlation between the HbA1c levels and the incidence of AKI in the studied patients (Figure 1). Multivariate linear regression analysis was used to define independent risk factors of AKI. According to regression analysis, HbA1c, 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, volume of CM, and blood glucose, HbA1c remained an independent risk factor for CI-AKI.

Discussion

Contrast-Induced Acute Kidney Injury (CI-AKI) is a prevalent but under diagnosed complication of PCI that is associated with increased in-hospital morbidity and mortality [3,18-20]. The importance of this complication is being increasingly recognized. Several recent North American and European epidemiological studies have shown that the incidence of AKI is increasing at an alarming rate [21]. Patients with DM, pre-existing renal insufficiency, congestive cardiac failure or advanced age are particularly susceptible to developing CI-AKI post-PCI.

The present study revealed that, elevated HbA1c levels were associated with increased incidence of CI-AKI in patients with T2DM (patients with an eGFR of ≥60 ml/min/1.73m 2) and STEMI undergoing PCI.

There are several previous reports demonstrated that acute hyperglycemia was associated with a significant increase of AKI following primary PCI [22,23]. Several studies have demonstrated that admission hyperglycemia in patients with STEMI increased the incidence of AKI, cardiac failure and mortality even in the absence of a history of T2DM [24-27].

The results of two recent studies regarding the relationship of admission hyperglycemia and CI-AKI are particularly interesting. These studies have demonstrated similar rates of CI-AKI development in T2DM patients with and without admission hyperglycemia [8,9]. However, the development of CI-AKI was more common in non-diabetic patients with admission hyperglycemia compared to those without admission hyperglycemia. The difference might possibly be explained by the administration of a more aggressive insulin therapy in patients with T2DM during hospitalization, a better hydration of these patients since T2DM is known to be a risk factor for CI-AKI, and the need for a greater stress factor in association with its secondary adverse effects in non-diabetics which generate a comparably high level of glucose.

Diabetes doubles the risk of developing AKI compared with non-diabetic patients. The incidence of AKI in diabetic patients varies from...
The increased incidence of AKI in diabetic patients has also been attributed to hypersensitivity of renal vessels of diabetics to adenosine, a vasoconstrictive agent, since experimental studies have shown increased adenosine-induced vasoconstriction in the kidneys of diabetic animals and the administration of adenosine receptor antagonists reduces the risk of development of contrast-Induced AKI in both diabetic and non-diabetic patients [29,30]. Moreover, hyperglycemia might cause hypovolemia by increasing the Osmotic Diuresis.

To date, there have been few studies on the relationship between long-standing poor glycaemic control and CI-AKI. In their retrospective study, Ding et al [31] have reported higher glycated albumin and HbA1c levels in patients with CI-AKI compared to those without CI-AKI (8.3±1.6% vs 7.5±1.2% for HbA1c, respectively, p<0.001). However, in this study, it might be incorrect to suggest uncontrolled glucose levels as the primary cause of CI-AKI. Since the rate of pre-existing Chronic Kidney Disease (CKD) was statistically significant compared to those without CI-AKI (p<0.001, for all). However, in our study, eGFR, age, LVEF, and CM volume were comparable between the two groups. In the other study, Yoshikawa et al [32] have reported a 5% increase in serum creatinine and a decrease of 4ml/min/1.73m² in eGFR in patients with an HbA1c of ≥6.5% compared to those with an HbA1c 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 repo by Akuyz et al [33] demonstrated no difference in the rate of AKI following elective PCI in Type-II diabetic patients undergoing elective PCI. Marenzi et al [23] demonstrated similar rates of AKI development following primary PCI in T2DM patients with and without admission hyperglycemia.

The results of the present study might be explained with the long and more marked effect of chronic intra-renal mechanisms on kidneys due to long-standing poor glycaemic control (i.e., changes in the intra-glomerular haemodynamics modulated in part by 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 [34].

Our study has several limitations: 1) Limited number of patients; 2) Urine albumin was not measured and as CKD is defined by an eGFR of ≥60 ml/min/1.73m² only in the presence of albuminuria for patients with T2DM, it can be presumed that some of the patients may not be appropriate; 4) These results might also not be valid for radiological procedures that use the intravenous rather than the intra-arterial route; 5) These results might not be valid for patients with Type-1 DM; and finally, 'hospital-induced nephropathy', a newly recognized aspect, described as a substantial day-to-day variation in serum creatinine in hospitalized patients regardless of CM injections, might have been a confounding factor [35].

Conclusion

In conclusion, an elevated HbA1c level is associated with a higher incidence of CI-AKI compared with an optimal HbA1c level in patients with T2DM (patients with an eGFR of ≥60ml/min/1.73m²) and STEMl undergoing CAG and/or PCI.

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