Introduction

Contrast-Induced Acute Kidney Injury (CI-AKI) is the third most common cause of in-hospital acute kidney injury (AKI) and accounts for 10% of total cases [1]. 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). A recent study evaluating the epidemiology of CI-AKI in over 8000 patients undergoing PCI found that CI-AKI occurred in 12% of STEMI, which was significantly higher compared with patients undergoing non-emergent catheterization (9.2% in unstable angina and NSTEMI patients and 4.5% undergoing elective PCI). Even in patients with baseline Glomerular Filtration Rate (GFR)>60, the incidence of CI-AKI in the STEMI patients was 9.2% [4]. Such a high incidence of this complication invokes the need to define measures to decrease the occurrence of CI-AKI in patients presenting with STEMI.

In addition to prophylactic intravenous volume expansion with isotonic crystalloid solution, few prophylactic strategies for CI-AKI are clearly effective [5]. The most important step in reducing the risk of CI-AKI is identifying at-risk patients as old age, Chronic Kidney Disease (CKD), Diabetes Mellitus (DM), hypertension, metabolic syndrome, hypovolemia, Congestive Heart Failure (CHF), an Ejection Fraction (EF) of less than 40%, hypotension, and Intra-Aortic Balloon Counterpulsation (IABP) use. Procedure-related risk factors are as urgent versus elective, arterial versus venous contrast. Contrast-related risk factors are as contrast volume, contrast characteristics, including osmolarity, ionicity, molecular structure, and viscosity. The single most important patient-related risk factor is preexisting CKD, even more so than DM [6]. Patients with CKD in the setting of DM...
have a 4-fold increase in the risk of CI-AKI compared with patients without DM or preexisting CKD [6].

The association between Hyperuricemia (HUA) and CI-AKI has not been extensively studied. It has been suggested that tubular obstruction by uric acid plays a role in the pathogenesis of CI-AKI [7,8]. HUA is accompanied by enhanced synthesis of Reactive Oxygen Species (ROS), activation of the renin-angiotensin-aldosterone system, an increase in Endothelin-1, and inhibition of the nitric oxide system; all of these factors play a role in the pathogenesis of CI-AKI [9-11]. However, there are no adequate clinical studies to demonstrate whether HUA further increases the risk of CI-AKI. Accordingly, in our study, we evaluated, the association between HUA and AKI occurrence in patients with normal kidney function and STEMI undergoing Coronary Angiography (CAG) and primary PCI.

**Patients and Methods**

This a prospective study conducted on 146 patients admitted during the period from January 2013 to April 2016 at National Heart Institute and Theodor Bilharz Research Institute, Cairo, Egypt, with acute STEMI for CAG and treated by PCI. STEMI was diagnosed as arterial occlusion by uric acid plays a role in the pathogenesis of CI-AKI [9].

According to Serum Uric Acid (SUA), patients were divided into 2 groups, normouricemic group (Group-I, n=68) and hyperuricemic group (Group-II, n=78). HUA was defined as SUA concentration of more than 7.0mg/dL in men and 6.0mg/dL in women [12].

SUA was measured on admission. Renal function tests (Serum Creatinine (Scr), blood urea, serum potassium, serum sodium) were measured on hospital admission, and at least once a daily. Random blood sugar, glycosylated hemoglobin (HbA1c), total cholesterol and triglycerides, C – Reactive Protein (C-RP), and Creatine Phosphokinase (C-PK) were measured from blood samples taken within 24h of hospital admission using standard methods. Echocardiography was used to measure LVEF. The eGFR was estimated using the abbreviated Modification of Diet in Renal Disease equation (MDRD). [13] Baseline renal insufficiency was categorized as admission eGFR of <60ml/min/1.73m². AKI was determined using Kidney Disease Improving Global Outcome (KDIGO) guidelines and defined as increase in Scr by 0.3mg/dl (26.5umol/l) within 48h of admission [14].

**Statistical Analysis**

All data were analysed as mean±standard deviation or as number (%). Continuous variables were compared using the independent sample t test (using GraphPad QuickCalcs). The p-values for the categorical variables were calculated with the chi square test. Spearman

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

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group-I (uric acid&lt;7mg/dL) No.68</th>
<th>Group-II (uric acid≥7mg/dL) No.78</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>57.8±11.4</td>
<td>60.7±12.5</td>
<td>0.1474</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>46/22 (67.6%/32.4%)</td>
<td>57/21 (73.1%/26.9%)</td>
<td>0.5856</td>
</tr>
<tr>
<td><strong>Systolic BLP (mm/Hg)</strong></td>
<td>130.9±24.7</td>
<td>135.8±27.6</td>
<td>0.2960</td>
</tr>
<tr>
<td><strong>Diastolic BLP (mm/Hg)</strong></td>
<td>87.8±19.2</td>
<td>89.7±19.3</td>
<td>0.5529</td>
</tr>
<tr>
<td><strong>Glucose level at admission (mg/dL)</strong></td>
<td>109.8±11.6</td>
<td>112.7±9.3</td>
<td>0.0990</td>
</tr>
<tr>
<td><strong>HbA1c (%)</strong></td>
<td>5.6±1.3</td>
<td>5.8±1.4</td>
<td>0.3749</td>
</tr>
<tr>
<td><strong>Total cholesterol (mg/dL)</strong></td>
<td>168.6±38.4</td>
<td>169.3±41.1</td>
<td>0.9159</td>
</tr>
<tr>
<td><strong>Triglycerides (mg/dL)</strong></td>
<td>87.8±15.9</td>
<td>89.2±21.3</td>
<td>0.6573</td>
</tr>
<tr>
<td><strong>Serum uric acid (mg/dL)</strong></td>
<td>6.23±0.73</td>
<td>6.92±1.87</td>
<td>0.0001</td>
</tr>
<tr>
<td><strong>Personal history of MI</strong></td>
<td>11(16.2%)</td>
<td>21(26.9%)</td>
<td>0.1743</td>
</tr>
<tr>
<td><strong>Family history of CAD</strong></td>
<td>18(26.5%)</td>
<td>31(39.7%)</td>
<td>0.1312</td>
</tr>
<tr>
<td><strong>No. of stenosed coronary arteries</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>19(23.4%)</td>
<td>18(23.1%)</td>
<td>0.8779</td>
</tr>
<tr>
<td>2</td>
<td>23(34.0%)</td>
<td>22(28.2%)</td>
<td>0.5605</td>
</tr>
<tr>
<td>3</td>
<td>26(42.6%)</td>
<td>38(48.7%)</td>
<td>0.5677</td>
</tr>
<tr>
<td><strong>Time to reperfusion (h)</strong></td>
<td>8.6±4.1</td>
<td>9.1±3.2</td>
<td>0.4099</td>
</tr>
<tr>
<td><strong>C-RP (mg/L)</strong></td>
<td>18.3±4.6</td>
<td>19.2±3.9</td>
<td>0.2028</td>
</tr>
<tr>
<td><strong>C-PK (units/L)</strong></td>
<td>1371.2±429.8</td>
<td>1425.3±469.2</td>
<td>0.4711</td>
</tr>
<tr>
<td><strong>LVEF (%)</strong></td>
<td>49.4±8.2</td>
<td>47.9±8.8</td>
<td>0.0701</td>
</tr>
</tbody>
</table>

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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Table 2: Serum creatinine changes, contrast media volume applied and the occurrence of AKI according to serum uric acid levels.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group-I (uric acid&lt;7mg/dL) N=68</th>
<th>Group-II (uric acid≥7mg/dL) N=78</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine at admission (mg/dL)</td>
<td>0.99±0.21</td>
<td>1.02±0.29</td>
<td>0.4810</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>78.31±17.2</td>
<td>74.62±13.9</td>
<td>0.1541</td>
</tr>
<tr>
<td>Contrast volume (mL)</td>
<td>138.6±16.7</td>
<td>141.3±17.2</td>
<td>0.3392</td>
</tr>
<tr>
<td>Serum creatinine 48h after PCI</td>
<td>1.28±0.56</td>
<td>1.62±0.74</td>
<td>0.0024</td>
</tr>
<tr>
<td>Serum creatinine at discharge</td>
<td>1.17±0.46</td>
<td>1.37±0.62</td>
<td>0.0304</td>
</tr>
<tr>
<td>AKI</td>
<td>2(2.94%)</td>
<td>11(14.1%)</td>
<td>0.0384</td>
</tr>
</tbody>
</table>

eGFR: Estimated Glomerular Filtration Rate; PCI: Percutaneous Coronary Intervention; AKI: Acute Kidney Injury

Discussion

Our study demonstrated that the incidence of CI-AKI was statistically significantly high in hyperuricemic patients compared with normouricemic patients (14.1% vs. 2.94%, p=0.0436) and the admission SUA level is correlated with the increased incidence of CI-AKI in patients with normal serum creatinine and acute STEMI undergoing PCI.

Previous reports have showed that elevated SUA is a risk factor for developing AKI in specific circumstances. Preoperative and postoperative HUA has been linked to a higher incidence of postoperative AKI, especially in cardiovascular surgery settings [15-19]. Moreover, HUA has also been shown to increase the risk of contrast-induced AKI after PCI [20,21]. SUA measurement has been proposed as a novel marker for early detection of AKI [22,23].

Toprak et al. conducted the most rigorous observational study of the value of HUA for predicting the risk of CI-AKI in patients with CKD (SCr≥1.2mg/dL) who were considered at high risk of developing CI-AKI and concluded that the hyperuricemic patients were at risk of developing CI-AKI [24]. The results of the present study were consistent with those obtained by Toprak and colleagues. Recently, Park et al. also concluded that HUA was independently associated with an increased risk of in-hospital mortality and CI-AKI in patients treated with PCI, although they performed a retrospective analysis that used a different definition of CI-AKI (an increase in SCr≥0.5mg/dL or ≥50% over baseline within seven days of PCI) [21]. Consequently, the incidence of CI-AKI in our study was lower than the incidence in previous studies [21,24].
The patients with normal SCr values, however, did not receive any prophylaxis, as they are typically thought to be at low risk. Chong et al. observed that subgroups of patients with normal baseline SCr who were undergoing PCI were at risk of developing CI-AKI, which results in higher mortality [25]. Therefore, despite normal baseline SCr values, the subgroups of patients undergoing PCI may be at higher risk of developing CI-AKI. In our study, HUA has been identified as one of independent risk predictor of CI-AKI in addition to age, LVEF and volume of CM. Hence, the patients with normal baseline SCr values who have the risk factors for CI-AKI should be considered for additional renal prophylaxis treatment.

In our study, the incidence of CI-AKI was statistically significantly high in hyperuricemic patients compared with normouricemic patients (14.1% Vs. 2.94%, p=0.0436) and no patients who developed AKI need renal replacement therapy. Our results are in agreement with the study of Liu et al. who concluded that the incidence of CI-AKI was significantly higher in the hyperuricemic group than in the normouricemic group (8.1% Vs. 1.4%, p<0.001) in patients with relatively normal serum creatinine after percutaneous coronary interventions. However, Liu et al demonstrated that, in hospital mortality and the need for renal replacement therapy were significantly higher in the hyperuricemic group [26].

There are many explanations for the increased AKI risk in patients with elevated SUA values. Uric acid has been proposed to play a role in AKI via crystal-independent mechanisms, as well as crystal-dependent pathways [27]. Elevated SUA can induce renal vasoconstriction and impair auto-regulation, which results in reduced renal blood flow and GFR. Sanchez-Lozada et al. showed that even a mild elevation of SUA can cause renal vasoconstriction in rats without evidence of intra-tubular crystal precipitation [27,30]. Furthermore, HUA has been shown to worsen renal injury via pro-inflammatory pathways involving chemokine expression with leukocyte infiltration, as well as proliferation of vascular smooth muscle cells and inhibition of endothelial function [28,31-33]. AKI-related crystal-dependent pathways can also occur in renal stones and acute urate nephropathy associated with tumor lysis syndrome [29,34-37].

The results of our study showed a prognostic effect of admission SUA level on the CI-AKI development. Previous attempts to identify effective interventions to prevent CI-AKI have been largely unsuccessful [38]. Using the admission SUA level in clinical practice may help identify patients with a high risk of CI-AKI during hospitalization in order to promptly prevent AKI events. Several clinical trials have examined the efficacy of uric acid-lowering agents, such as allopurinol, in cardiovascular surgery and found a reduction in the production of ROS [39,40]. Rasburicase has also been studied in a prospective, double-blind, placebo-controlled, randomized trial of 26 hyperuricemic patients undergoing cardiac surgery [41]. Despite no observed benefit on postoperative SCr, markers of structural renal injury such as urine neutrophil-associated lipocalcin tended to be lower in rasburicase-treated patients.

Conclusion

Our study has some limitations. First, this is a single-center, prospective study. Second, small sample of patients is included in our study, so further bigger multicenter prospective studies are required to address these limitations.

In conclusion, this study showed that elevated admission SUA is associated with an increased risk of CI-AKI in patients with STEMI and normal SCr undergoing PCI.

References


