Incidence of Contrast Induced Nephropathy in Patients with Type 2 Diabetes Mellitus and its Association with Glycosylated Hemoglobin (HbA$_{1c}$) Level and Duration of Diabetes

Eddy Chandra, MD* and Margrette Ruth Lampa-Bernardo, MD*

**ABSTRACT**

**Background:** Contrast Induced Nephropathy (CIN) is the third leading cause of hospital-acquired acute kidney injury. Patient with diabetes mellitus is associated with higher risk for CIN but association with the duration of diabetes and Glycosylated Hemoglobin (HbA$_{1c}$) level is still unclear.

**Objective:** To determine the incidence of CIN and whether duration of diabetes and HbA$_{1c}$ level were associated with the occurrence of CIN among diabetic patients.

**Methods:** This is a retrospective cross-sectional analytic study. 186 diabetic patients who underwent CT scan of the chest, abdomen, and cranial CT-angiogram with intravenous contrast from January 2010 to June 2015 were included. Stepwise regression analysis was done to confirm their association with CIN.

**Results:** The incidence of CIN was 30.1%. No significant differences in age, gender, BMI, and baseline creatinine between the CIN positive and negative groups. However, the eGFR was lower (69.1±30.8 vs 79.1±23.2 ml/min/1.73m$^2$, $p=0.017$) in the CIN positive group. Pre-existing kidney disease was associated with the development of CIN ($p=0.002$). The duration of diabetes was not significantly associated with the occurrence of CIN ($p=0.157$). However, HbA$_{1c}$ level $\geq$7% was significantly associated with the development of CIN (OR [95%CI] =20.15 [8.558 to 47.449], $p=0.0001$). The multivariate analysis confirmed the association of the HbA$_{1c}$ level $\geq$7% with the development of CIN after adjustment for baseline confounding factors (adjusted OR [95%CI] = 20.12 [8.17 to 49.53], $p=0.0001$).

**Conclusion:** The incidence of CIN post contrast enhanced CT scan in diabetic patient was 30.1%. HbA$_{1c}$ level $\geq$7% was significantly associated with higher risk of CIN among patients with type 2 diabetes mellitus.

**Key words:** contrast induced nephropathy, diabetes mellitus, acute kidney injury, HbA
INTRODUCTION
The increased utilization of radiographic procedures for diagnosis and treatment led to the increased use of contrast media. Some complications may occur from the use of contrast media. One most common complication is Contrast Induced Nephropathy (CIN). There are 6,000 diagnostic and 2,000 therapeutic cardiac catheterizations performed yearly per million inhabitants in western countries. In parallel, the incidence and prevalence of CIN has also risen. CIN currently is the third leading cause of hospital-acquired Acute Kidney Injury (AKI). It is also associated with prolonged hospitalization, high morbidity and in-hospital mortality. McCullough et al. (1997), in their epidemiological study reported that the incidence of acute kidney injury after coronary intervention was 14.5% and 0.7% required dialysis. The incidence of CIN varies depending on the definition used, risk factors, type and volume of contrast and type of procedure. In patients without any risk factors, CIN incidence was reported to be at 2-3%. In high-risk patients, such as patients with chronic renal impairment, diabetes mellitus, congestive heart failure, and older age, the incidence reported was 20% to 30%.

Some risk factors have been identified to increase risk to develop CIN. Mehran et al. (2006), in their study concluded that the risk factors for the development of CIN can be divided into modifiable and non-modifiable risk factors. Modifiable risk factors include volume and type of contrast media, concomitant use of nephrotoxic medications, hypotension, dehydration, hypoalbuminemia, anemia, and the use of intra-aortic balloon pump (IABP). Non-modifiable risk factors include pre-existent renal insufficiency, diabetes mellitus, older age, reduced left ventricle systolic function, advanced heart failure, acute myocardial infarction, and shock. The most important risk factor is preexisting renal impairment.

The presence of Chronic Kidney Disease (CKD) with diabetes showed significantly higher risk of developing CIN. CIN incidence among diabetic patient with concomitant kidney disease was reported to be 9-90%. CIN incidence of 9-40% was seen in diabetic patients with mild to moderate chronic kidney disease and 50-90% in those with severe chronic kidney disease. Glycosylated Haemoglobin (HbA1c) is a simple blood examination and widely used to assess glycemic control in patients with diabetes mellitus. The association between HbA1c level with kidney disease has been shown in some studies. Hernandez et al. (2013), reported that an increase in HbA1c was associated with a 30% to 40% increase in the rate of CKD or Cardiovascular Disease (CVD), with the HbA1c optimal predictor cut-off value of 5.5%. National Kidney Foundation KDOQI Clinical Practice guideline for Diabetes and CKD 2012 recommend a target HbA1c of 7.0% to prevent or delay progression of microvascular complications of diabetes, including Diabetic Kidney Disease (DKD).

Duration of diabetes is an important factor in the development of nephropathy. The longer duration of diabetes confers a higher risk to develop nephropathy. Inassi J, et al. (2013), reported that as duration of diabetes increases, there is impairment of renal function as well.

The association between HbA1c level and duration of diabetes with the development of CIN is unclear. A study done by Akyus S, et al. (2014), did not show higher incidence of CIN in those with elevated HbA1c level compared to those with optimal HbA1c level among type 2 DM patients. However, association is reported in other studies. In the study done by Barbieri L et al. (2014), there is a linear association between incidence of CIN and HbA1c level (p=0.001) in pre-
diabetic patients. There was also a study done in non-diabetic patients which showed association as well.

**Literature Review**

Contrast Induced Nephropathy according to KDIGO 2012 is defined as either a serum creatinine (SCr) increase > 0.5 mg/dl (>44 µmol/l), or a SCr increase >25% or a decrease >25% of eGFR, or the composite of all three definitions after systemic contrast medium administration. Typically, CIN onset occurs within 48-72 hours of exposure, although it has been suggested that in patients with renal insufficiency, CIN may occur up to 7 days post-contrast administration. Serum creatinine levels peak in 3-5 days, and renal function returns to baseline in 7-21 days. The incidence of CIN is low (1-2%) in patients with normal renal function even with the presence of diabetes. However, in patients with preexisting renal impairment or in presence of risk factors such as combination of CKD and diabetes, Congestive Heart Failure (CHF), advanced age and concurrent administration of nephrotoxic drugs the incidence may be as high as 25%. Based on the Canadian Association of Radiologist (2011) Consensus Guidelines for the Prevention of Contrast Induced Nephropathy, a follow-up serum creatinine measurement is recommended 48 to 72 hours after contrast media injection in patients who have risk factors for developing CIN especially in patient with eGFR below 45 mL/min.

Numerous studies have identified predisposing risk factors for CIN. These risk factors can be divided into patient and procedural related risk factors. Patient related risk factors are baseline creatinine level, diabetes mellitus, female, advanced age (>70), nephrotoxic medications (Chronic use of nonsteroidal anti inflammatory drugs (NSAIDS), aminoglycosides, vancomycin, amphotericin B, immunosuppressive medications such as cyclosporine, and loop diuretics), anemia, acute coronary syndrome, volume depletion, low cardiac output, intra aortic balloon pump use, congestive heart failure, renal transplant patient, hypoalbuminemia and multiple myeloma. Procedural factors are contrast agent amount, osmolarity of contrast agents, and multiple contrast media application within 72 hours. After thorough research, there were no similar local studies found.

The pathophysiology of CIN is complex and not fully understood. In patients with type 2 diabetes mellitus CIN develop due to multiple factors. The primary factor of which is coexisting chronic renal disease. Furthermore, there is an association of other factors such as endothelin and intrarenal adenosine in the development of CIN. Endothelin and intrarenal adenosine are potent arteriolar vasoconstrictor which are released after administration of contrast media leading to decrease in glomerular filtration rate (GFR).

**METHODS**

**Study Design**

This is a 5-year retrospective cross sectional analytic study performed at a tertiary teaching hospital De La Salle University Medical Center in Dasmariñas, Cavite, Philippines (Figure 1).

**Study Population**

The study population consists of all adult patients (age ≥18 years old) who have type 2 diabetes mellitus and underwent CT Scan of the Chest, abdomen and Cranial CT angiography with intravenous contrast media at DLSUMC between January 2010 and June 2015.
**Time and Duration of Study**
The data collection, processing, and analysis were conducted between August 2015 and March 2016.

**Sample Size**
The minimal sample size is 147 subjects calculated at 95% confidence level and assuming incidence of CIN is 25%±7%. The incidence is based on study of Wang XC\(^{25}\) and KDIGO guidelines (2012).\(^{17}\)

**Measurements**
All the demographic data and variables were collected by the investigator retrospectively by chart review retrieved from the medical records section.

Primary outcome is the incidence of CIN. CIN is defined as 25% increase in serum creatinine from baseline or 0.5 mg/dL (44 µmol/L) increase in absolute value within 48-72 hours after injection of contrast administration.

**Inclusion and Exclusion**

**Inclusion Criteria**
- Adult patient (>18 years old)
- Diagnosed with type 2 diabetes mellitus from history taking
- Underwent CT scan of the chest and whole abdomen with Intravenous contrast media and cranial CT angiography with intravenous contrast media.
- All procedures would require similar amount of contrast hence they were included in the study.

**Exclusion Criteria**
- Pregnant patient
- End Stage Renal Disease (ESRD) on dialysis patient
- Hemoglobin level ≤10 g/dl, because anemia will interfere the Hba\(_{1c}\) test result.
- Incomplete medical record

**Data Analysis**
All data of study subjects were collected through chart review of history taking and diagnostic (laboratory and radiologic) results. In this study, 10-year duration of diabetes will be used as cut off based on the study by Inassi J, et al. (2013), which revealed that the serum creatinine was significantly increased in both gender with diabetes of more than 10-year duration.\(^{14}\)

We computed the incidence of CIN among diabetic patients from the total number of subject who had CIN divided by total number of population. All variables from patients who had CIN were compared with those not having CIN by using univariate analysis (χ\(^2\) square test for categorical data, such as gender, BMI, duration of diabetes, Hba\(_{1c}\) level, CIN positive or negative, history of hypertension, heart disease and preexisting kidney disease; independent’s t-test for numerical data, such as age, BMI, serum creatinine level and eGFR).

The association between glycosylated hemoglobin and duration of diabetes with the occurrence of CIN were confirmed by multivariate analysis after correction for baseline confounding factors. \(P\) values <0.05 were considered as statistically significant.

**RESULTS**

**Incidence of CIN**
Result showed that 56 out of 186 subjects developed Contrast Induced Nephropathy with overall proportion of 30.1 % with 95% confidence interval of 23.73% to 37.33%.

**Profile**
The 2 groups did not differ significantly (\(p\) values >0.05) in terms of age, gender, BMI, and baseline serum creatinine level (Table 1). The eGFR baseline is significantly lower in subjects who develop CIN with \(p\)
value 0.017.

<table>
<thead>
<tr>
<th>Profile</th>
<th>CIN Positive (n=56)</th>
<th>CIN Negative (n=130)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean±sd</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥70 year old</td>
<td>62.0±12.4</td>
<td>61.1±11.2</td>
<td>0.658</td>
</tr>
<tr>
<td>Female, gender</td>
<td>16 (28.6)</td>
<td>29 (22.3)</td>
<td>0.202</td>
</tr>
<tr>
<td>BMI (kg/m²), mean±sd</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underweight</td>
<td>0 (0.0)</td>
<td>1 (0.8)</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>14 (25.0)</td>
<td>28 (21.5)</td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>14 (25.0)</td>
<td>30 (23.1)</td>
<td>0.834</td>
</tr>
<tr>
<td>Obese Class I</td>
<td>26 (46.4)</td>
<td>62 (47.7)</td>
<td></td>
</tr>
<tr>
<td>Obese Class II</td>
<td>2 (3.6)</td>
<td>9 (6.9)</td>
<td></td>
</tr>
<tr>
<td>Serum Creatinine (mmol/L) baseline, mean±sd</td>
<td>107.4±60.0</td>
<td>91.5±64.3</td>
<td>0.151</td>
</tr>
<tr>
<td>eGFR baseline (ml/min/1.73m²), mean±sd</td>
<td>69.1±30.8</td>
<td>79.1±23.2</td>
<td>0.017</td>
</tr>
</tbody>
</table>

**Comorbidity**

Hypertension and heart disease were not significantly associated with the occurrence of CIN. On the other hand, preexisting kidney disease is significantly associated with the occurrence of CIN (p=0.002) (Table 2).

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>CIN Positive (N=56) n (%)</th>
<th>CIN Negative (N=130) n (%)</th>
<th>Odds Ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>38 (67.9)</td>
<td>79 (60.8)</td>
<td>1.363 (0.703 to 2.643)</td>
<td>0.360</td>
</tr>
<tr>
<td>Heart Disease</td>
<td>10 (17.9)</td>
<td>19 (14.6)</td>
<td>1.270 (0.549 to 2.940)</td>
<td>0.578</td>
</tr>
<tr>
<td>Preexisting Kidney disease</td>
<td>10 (17.9)</td>
<td>4 (3.1)</td>
<td>6.848 (2.047 to 22.912)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

**HbA1c level and Duration of Diabetes**

The duration of diabetes is not significantly associated with the occurrence of CIN (p=0.157) (Table 3).

**DISCUSSION**

This study showed that there is 30.1% incidence of Contrast Induced Nephropathy (CIN) among type 2
diabetes mellitus admitted at DLSUMC from 2010-2015. The result was consistent with the literature, which showed the incidence of CIN among high risk patients (e.g. patients with chronic renal impairment, diabetes mellitus, congestive heart failure, old age) as more than 20% to 30%.

Pre-existing kidney disease was associated with the occurrence of CIN in this study which was shown in the univariate analysis. This result is similar to the study done by Subedi et al. (2011), who compared the incidence of CIN between patients with and without preexisting chronic renal insufficiency. It revealed that 21.7% of patients with preexisting chronic renal insufficiency developed CIN which was significantly higher compared to those without preexisting renal problem at 6.3% (p=0.003). The development of CIN in patients with pre-existing kidney disease caused by diabetes can be explained by the enhanced reactive oxygen species (ROS) generation, altered nitric oxygen (NO) response and reduced oxygen tension (PO2). The intravascular administration of contrast media further reduces medullary PO2 by enhancing formation of ROS and with oxidative and nitrosative stress induced cellular hypoxic stress response hence predisposing to CIN.

The duration of diabetes was not significantly associated with the occurrence of CIN in this study. Although some literature showed a higher risk for kidney disease with longer duration of diabetes, this may not solely explain the development of nephropathy. Other factors should be highly considered such as glycemic control in predicting the risk for progression of kidney disease.

In this study, Glycosylated hemoglobin (HbA1c) level ≥7% shows a significant association with the incidence of CIN on univariate analysis which is confirmed by multivariate analysis after adjustment for confounding factors. The results were similar to a study done by Barbieri et al. (2014), which showed linear association between glycated hemoglobin levels and the risk of CIN. Results revealed that poor glycemic control reflected by the higher HbA1c level is an important factor in the development of nephropathy in patients with type 2 diabetes mellitus and a higher risk for CIN as well.

**Limitations and Recommendations**

The retrospective data gathering from chart review is prone to recall bias and missing data. Being conducted in a single center poses to be an additional limitation of this study. Hence, to be able to get a better representation of the population, it is recommended that this study should be conducted in a multicenter setting.

During data collection, it was found out that the amount and type of agent used as prophylaxis varied among patients included in the study thus this parameter was not included in the study. It is highly recommended that a uniform amount and type of agents be used as prophylaxis to eliminate bias.

**CONCLUSION**

Among patient with type 2 diabetes mellitus, the incidence of Contrast Induced Nephropathy (CIN) is 30.1%. Duration of diabetes is not statistically significant with the occurrence of CIN. Glycosylated Hemoglobin (HbA1c) level ≥7.0% is significantly associated with higher risk for developing CIN.

**Acknowledgment**

None.

**Funding**

None.

**Disclosure**

None.

**About the Paper**

This paper has been presented at the 33rd World Congress of Internal Medicine (WCIM), August 22-25, 2016, Bali, Indonesia (Poster Presentation) and at the 47th Annual Convention of the Philippine College of Internal Medicine.
of Physicians (PCP), May 7-10, 2017, SMX Mall of Asia, Manila. It has also been awarded the first prize for Retrospective Analytical study design for the 2017 Most Outstanding PCP Researches.

Author Details
Eddy Chandra MD; Former Internal Medicine Resident, Department of Internal Medicine, De La Salle University Medical Center, Dasmariñas, Philippines
Margrette Ruth L. Bernard, MD; Active Medical Staff, Department of Internal Medicine, De La Salle University Medical Center, Dasmariñas, Philippines

REFERENCES


