Contrast Induced Nephropathy in Diabetic and Non Diabetic Patients After Coronary Intervention

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Abstract

Background
A rise in contrast enhanced diagnostic imaging and interventional procedures has been observed especially in diabetic patients which was accompanied by the increased risk of contrast induced nephropathy which negatively impacts the prognosis of those patients.

Contrast induced nephropathy is an important cause of acute renal failure and this form of nephropathy has become the third leading cause of hospital-acquired acute renal failure.

In patients with type 2 diabetes mellitus complications develop 3 times more often, than in patients without diabetes. In high risk groups elderly patients with type 2 diabetes mellitus and previous history of nephritic pathology, anemia and heart failure, the probability of contrast induced nephropathy remains considerable, despite use of low toxic contrast agents and sufficient hydration.

Objective
The present study aimed to compare the effect of contrast media on renal function of Iraqi patients after therapeutic coronary intervention for patients without type 2 diabetes mellitus and patients with type 2 diabetes mellitus

Materials and Methods:
Forty two patients participated in the study. They were divided into two groups as follow:

Group A: twenty two patients (12 males and 10 females) without type 2 diabetes mellitus.

Group B: twenty patients (12 males and 8 females) with type 2 diabetes mellitus.

The type 2 diabetic patients classified into four groups according to the drug(s) that used for treatment of diabetes:

♦ 13% of them were treated by insulin.
♦ 25% were treated by dietary regimen and sulfonyl urea.
♦ 14% were treated by metformin.
♦ The remaining were treated by glinides plus biguanides.

All patients involved in the study were given low osmolar non-ionic contrast media Omnipaque (Iohexol). The study lasted about three months at Shaheed Al- Mihrab Center for Cardiac Catheterization under supervision of specialist interventional cardiologist.

Clinical and laboratory examinations were measured before the percutaneous coronary intervention. Renal function tests including serum creatinine and serum urea were measured before and after percutaneous coronary intervention.

Contrast induced nephropathy was defined as a rise in serum creatinine of 0.5 mg/dL (29.7 µmol/L) or a 25% increase from the baseline values, assessed at 48 hours of the percutaneous coronary intervention.

Results
1. Contrast media caused more significant increase in serum creatinine level in patients with type 2 diabetes mellitus than in patients without type 2 diabetes mellitus. Moreover, the incidence of contrast induced nephropathy in diabetic patients developed three times more often than in non-diabetic patients.
2. Contrast media caused a significant increase in serum urea in patients with type 2 diabetes mellitus, whereas in patients without type 2 diabetes mellitus, serum urea did not significantly change.
3. Contrast media caused more significant decrease in glomerular filtration rate in patients with type 2 diabetes mellitus than in patients without type 2 diabetes mellitus.
4. Contrast media caused a significant decrease in creatinine clearance level in patients with type 2 diabetes mellitus, while in patients without type 2 diabetes mellitus, creatinine clearance did not significantly change.

Conclusion: The present study demonstrates that diabetic patients are susceptible to higher risk of contrast induced nephropathy than non-diabetic patients

Key Words: Contrast induced nephropathy, coronary angiography, Diabetes mellitus
 Malka Abu Kwaym

1. Introduction

1.1 Diabetes Mellitus

Diabetic patients represent a significant proportion of patients undergoing contrast procedures. The incidence of contrast induced nephropathy (CIN) in diabetic patients varies from (5.7) to (29.4%) (Rother, 2006; Tremont et al., 2007).

Clinically important CIN usually occurs in a subset of diabetic patients with underlying renal insufficiency (Fowler, 2007; Mehran et al., 2004).

Diabetes mellitus is one of the most important risk factors of renal function disorders after contrast media intervention (Rudnick and Goldfarb, 2003). In high risk
groups [elderly patients with type 2 Diabetes mellitus (T2DM) and previous history of nephritic pathology, anemia and heart failure] CIN morbidity reaches 30% (Barrett and Parfrey, 2006). In patients with T2DM complications develop 3 times more often, than in patients without diabetes (Ogi et al., 1998).

1.2. Nephropathy:
Is partial loss of function of kidney associated with nephrotic syndrome, glomerulosclerosis, persistent albuminuria, declining glomerular filtration rate (GFR), and fluid retention (Casey et al., 2004; Kurus et al., 2005).

1.3. What is Contrast Induced Nephropathy?
CIN is defined as a rise in serum creatinine by 25% or greater than 0.5mg/dl (44µm/l) from baseline or fall in glomerular filtration rate by 25% after contrast administration in the absence of other causes (Rich and Crecelius, 1990). CIN occurs within 24–48 hours of exposure to CM, serum creatinine levels peak in 3–5 days, and renal function returns to baseline in 7–21 days. The incidence of CIN is less than 5% in patients with normal renal function and 15–50% in patients with baseline creatinine clearance (Cr.Cl) less than 60mL/min (Rich and Crecelius, 1990). This form of nephropathy has become the third leading cause of hospital-acquired acute renal failure, accounting for 12% of all cases (Brezis and Epstein, 1989). Affected patients may require short-term hemodialysis, which can extend their hospital stay and increase the risk of permanent impairment of renal function (Dangas et al., 2005).

CIN is associated with elevation of serum creatinine, within 48–72 hrs after injection of iodine contrast media (ICM) (Alwall et al., 1955). Prevention of CIN is essentially important in view of improving quality of life (Rudnick et al., 1995).

1.3.1. Iodine Contrast Media
As early as the 1950 it was recognized that ICM, could be nephrotoxic (Carraro et al., 1998). Low-osmolar ICM shown to be less nephrotoxic than high-osmolar agents (Murakami et al., 1998; Kozak et al., 2006).

1.3.2. Type of Iodine Contrast Media:
types of ICM are:
1- Ionic- monomeric high-osmolar contrast media. (e.g. diatrizoate).
2- Non-ionic monomeric contrast media (e.g. ionic mono-acidic dimeric contrast media. Low-osmolar (ioxaglate) or iohexol, iopromide)
3- Non-ionic dimeric iso- osmolar (iodixanol) , thus, low- or iso-osmolar CM should be used in patients at risk of CIN (Kozak et al., 2006).

Table (1-1) : Radiographic Contrast Agents (Barrett, 1994).

<table>
<thead>
<tr>
<th>Product</th>
<th>Type of Contrast Agent Concentration</th>
<th>Mg(1/ml)</th>
<th>Osmality(mOsm/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monomers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iohexol(Omnipaque)</td>
<td>Nonionic LOCM</td>
<td>350</td>
<td>844</td>
</tr>
<tr>
<td>Iopamidol(Isovue)</td>
<td>Nonionic LOCM</td>
<td>350</td>
<td>796</td>
</tr>
<tr>
<td>Ioxilan</td>
<td>Nonionic LOCM</td>
<td>370</td>
<td>695</td>
</tr>
<tr>
<td>Iopromide(Ultravist)</td>
<td>Nonionic LOCM</td>
<td>350</td>
<td>744</td>
</tr>
<tr>
<td>Ioversol(Optiray)</td>
<td>Nonionic LOCM</td>
<td>350</td>
<td>792</td>
</tr>
<tr>
<td>Dimers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iodixanol (Visipaque)</td>
<td>Nonionic IOM</td>
<td>320</td>
<td>290</td>
</tr>
<tr>
<td>Ioxaglate (Hexabrix)</td>
<td>ionic LOCM</td>
<td>320</td>
<td>600</td>
</tr>
</tbody>
</table>

LOCm, Low-osmolar contrast media; IOM, Iso-osmolar contrast media

1.3.3. Renal Handling of Contrast Media
The elimination half-life in patients with normal renal function is about 2 hrs and 75% of the administered dose is excreted in urine within 4 h. After 24 hrs 98% of
the injected contrast media are out of the body. Contrast medium induced Diuresis will cause an increase in intratubular pressure, which will cause reduction in the glomerular filtration rate (Katzberg et al., 1977).

1.3.4. Contrast Induced Nephropathy Pathogenesis :

The cellular changes which occurs after exposure to radio contrast dye are:

A. Renal Hemodynamic Changes : It has been suggested that the development of contrast-medium nephropathy is affected by changes in renal hemodynamic because of the effects of the contrast medium on the action of many substances, including increased activity of renal vasoconstrictors (vasopressin, angiotensin II, dopamine-1, endothelin and adenosine) and decreased activity of renal vaso-dilators (nitric oxide and prostaglandins) (Nygren and Ulfendahl, 1989; Liss et al., 1996; Ueda et al., 1993).

B. Direct Toxic Effect on Renal Cells: Pathological changes induced by contrast medium (e.g., epithelial cell vacuolization, interstitial inflammation and cellular necrosis) suggest a direct toxic effect of contrast media on renal tubular epithelial cells (Andrade et al., 1993; Paller and Manivel, 1992).

C. Endothelial Dysfunction : It has not been shown that contrast media-induced haemodynamic alterations of the renal vessels are directly related to the synthesis and release of active mediators such as nitric oxide and prostaglandins, although their active role in the regulation of renal perfusion is well known. The intrarenal production of these vasodilators is responsible for the maintenance of perfusion and oxygen supply in the medulla; therefore, reductions in the availability of these mediators can promote nephropathy (Heyman et al., 1992).

D. Effect of Osmolality : Experimental evidence has shown that hyperosmolar contrast media induce renal hemodynamic changes and have direct toxic effects on renal epithelial cells. Non-contrast hyperosmolar solutions, such as saline and mannitol, can cause renal vasoconstriction, which results in reductions in renal blood flow and the glomerular filtration rate than reductions seen with contrast media (Liss et al., 1998; Lancelot et al., 2002). Recently, it has been shown that iso-osmolar agents may be even less nephrotoxic than hypo-osmolar agents in such patients.

1.3.5. Clinical presentation :
The serum creatinine level begins to rise within 24 hours after administration of a contrast medium in 80% of patients in whom contrast medium nephropathy develops (Love et al., 1994; Toprak et al., 2004). In patients with severe renal failure necessitating a prolonged hospital stay or dialysis, the serum creatinine level almost always increases within the first 24 hours typically peaking on the second or third day after administration of the contrast medium and returning to baseline values within 2 weeks.

1.3.6. Radiographic Features of Contrast Induced Nephropathy

Persistent nephrogram on plain radiography of the abdomen for 24–48 hours post contrast media injection has been described as a feature of CIN (Artunc et al., 2005).

1.3.7. Risk Factors for Contrast Induced Nephropathy

Specific factors that increase the risk of developing CIN are related to the patient, the CM, and the procedure (Rihal et al., 2002; Parfrey et al., 1989). Mehran et al developed a simple scoring method that integrates eight baseline clinical variables to assess the risk of CIN after percutaneous coronary intervention (PCI). These are hypotension (score 5), the use of an intra-aortic balloon pump (score 5), congestive heart failure (score 5), a serum creatinine level ≥ 1.5 mg/dl (score 4), age >75 years (score 4), anemia (score 3), diabetes mellitus (score 3), and the volume of CM (score1/100 ml). If the total score is 5 or less, the risk category is low; if the total score is 16 or higher, the risk category is very high.
A-Patient Related Risk Factors :-

The most common patient-related risk factors are:

- Preexisting renal disease,
- Diabetes mellitus,
- Older age,
- Congestive heart failure, reduced left ventricular ejection fraction, hypertension, low hematocrit level, hyperuricemia, hypovolemia, low serum albumin level, renal transplantation, multiple myeloma, nephrotoxic drugs.

B-Contrast Media Related Risk Factors

1-VOLUME OF CONTRAST MEDIA: Some studies found a correlation between the volume of contrast given and the risk of nephropathy. The limit was 5 mL of contrast per kg of body weight up to a maximum of 300 mL, divided by the serum creatinine concentration in milligrams per deciliter.

2-OSMOLARITY: The use of an isoosmolar contrast medium (LOCM) substantially reduces the risk of nephropathy in high-risk patients compared with the use of high osmolar contrast medium (HOCM) (Modi and Rao, 2001).

1.3.8. Diagnosis of Contrast Induced Nephropathy:

The primary differential diagnoses include ischemic ATN and renal atheroembolic disease (Modi and Rao, 2001; McCullough et al., 1997). Urinary indices in CIN often demonstrate a fractional excretion of sodium of < 1%, whereas ischemic ATN is typically associated with a fractional excretion of sodium of > 1% (McCullough et al., 1997). Examination of the urine sediment in both conditions demonstrates coarsely granular “muddy brown” casts. Atheroembolic disease usually has a later onset following intravascular manipulation, occurring days to weeks following the procedure compared with hours to days for CIN. Atheroembolic disease is also often associated with systemic manifestations including mesenteric ischemia, digital ischemia (“blue toe syndrome”), and livedo reticularis (Modi and Rao, 2001; McCullough et al., 1997).

1.3.9. Prevention of Contrast Induced Nephropathy

A-Modification of Risk Factors :

When possible, the administration of contrast media should be delayed in patients with circulatory collapse or congestive heart failure until their hemodynamic status is corrected. If nephropathy develops, repeated exposure should be delayed until the patient’s serum creatinine level has returned to baseline levels (McCullough et al., 1997; Solomon et al., 1994). NSAIDs, diuretics and possibly ACE inhibitors should be discontinued 1–2 days before administration of contrast media most importantly, the smallest possible amount of nonionic, hypo-osmolar or iso-osmolar CM should be used in patients with risk factors (McCullough et al., 1997; Solomon et al., 1994).

B-Therapeutic Approaches Evaluated in Clinical Trials:

1-Saline Hydration and Forced Diuresis :- A standardized saline hydration protocol has been proven effective in reducing the risk of contrast-medium nephropathy and should be used routinely. The incidence of nephropathy was significantly lower among patients who received saline alone 11% than among those who received saline plus mannitol 28% or saline plus furosemide 40% (Solomon et al., 1994; Bakris et al., 1999).

2-Vasodilators

A. Fenoldopam is a selective dopamine-1 receptor agonist that produces systemic, peripheral and renal arterial vasodilatation. It causes a decrease in renal vascular resistance and increases in renal blood flow, glomerular filtration rate, and sodium and water excretion (Chamsuddin et al., 2002).

B. Adenosine antagonists: Contrast media stimulate the intrarenal secretion of adenosine, which binds to the renal adenosine receptor and acts as a potent
vasoconstrictor, reducing renal blood flow and increasing the generation of oxygen free radicals as it is metabolized to xanthine and hypoxanthine (Chamsuddin et al., 2002; Tepel et al., 2000).

3- Antioxidants: N-acetylcysteine: It reduces renal damage by scavenging oxygen free radicals, generated as a result of toxic damage to renal tubules N-acetylcysteine may also have direct vasodilating effects on the kidneys through an increase in the biologic effects of nitric oxide, which is a potent and stable vasodilator contributing to improved renal hemodynamics (Tepel et al., 2000).

4- Hemodialysis or Hemofiltration: an increase in serum creatinine levels was significantly less common in patients randomly assigned to prophylactic hemofiltration before and after the administration of CM than in those assigned to receive fluid alone. In-hospital death was also significantly less frequent (Sterner et al., 2000; Lehnert et al., 1998).

5- Renal Replacement Therapy: A series of studies have examined the use of conventional hemodialysis following the administration of CM (Berger et al., 2001). No beneficial outcomes were seen, and trends toward an increased need for therapeutic hemodialysis as well as a higher incidence of renal failure were observed in some of studies (Berger et al., 2001).

2. Materials and Methods

2.1. Patients:
The study was conducted over three months from the first of July to the first of October 2012. The patients were selected from "Shaheed Al-Mihrab Center for cardiac catheterization in Babil city" under. Forty two patients participated in the study. They were grouped into:

Group A: twenty two patients (12 males and 10 females) without T2DM.

Group B: twenty diabetic patients (12 males and 8 females) with T2DM.

The mean duration of diabetes was 11.3±6.33 (range: 3-24) years.

The diabetic patients were previously diagnosed according to World Health Organization definition of diabetes, as fasting plasma glucose ≥ 7.0 mmol/L (126 mg/dL) or 2-hour post-load plasma glucose ≥ 11.1 mmol/L (200 mg/dL) Hashemi et al., 2005. The type 2 diabetic patients classified into four groups according to the drug(s) that used for treatment of diabetes: 13% of them were treated by insulin; 25% were treated by dietary regimen and sulfonylurea; 14% were treated by metformin; The remaining were treated by glinides plus biguanides.

2.2. Inclusion / Exclusion criteria

2.2.1. Inclusion criteria: For group A, non diabetic patients with base line serum creatinine <1.5 mg/dl, normal renal function and normal liver function were included in the study. For group B, diabetic patients with T2DM, base line serum creatinine <1.5 mg/dl, normal renal function and normal liver function were included in the study. All the patients entered the center for therapeutic coronary intervention, the patients characteristics are shown in Table (2-1).

2.2.2. Exclusion criteria: Patients with following characteristics were excluded:

Preexisting renal failure, acute myocardial infarction before 24hrs from exposure to contrast media, serum creatinine >1.5mg/dl, age > 75 years, GFR < 60 ml/min, multiple myeloma, diastolic hypotension (BP ≤ 70 mm Hg), contraindications for invasive procedures, signs of infection, hypertriglyceridemia, history of hypersensitivity to contrast agents, breast-feeding, pregnancy, sepsis, renal artery stenosis, congestive heart failure, hypercholesterolemia, hypoalbuminemia, structural
kidney disease or damage, treatment with antibiotic, cirrhosis of the liver, nephrotic syndrome, anemia, cancer, hyperuricemia, protein urea and renal transplant.

### Table (2-1): Patients Characteristics Participated in the Study

<table>
<thead>
<tr>
<th>Demographic Variables</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>22</td>
<td>20</td>
</tr>
<tr>
<td>Age (years) Mean ± SD</td>
<td>55.13±1.95</td>
<td>55.62±6.15</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>12/10</td>
<td>12/8</td>
</tr>
<tr>
<td>Height (cm) Mean ± SD</td>
<td>164 ±7.77</td>
<td>162.80±5.76</td>
</tr>
<tr>
<td>Weight (kg) Mean ± SD</td>
<td>74.72±10.35</td>
<td>72.83±9.07</td>
</tr>
<tr>
<td>BMI (kg/m²) Mean ± SD</td>
<td>28.82±4.64</td>
<td>28.10±4.14</td>
</tr>
<tr>
<td>SBP (mmHg) Mean ±SD</td>
<td>133.54±19.3</td>
<td>136.90±25.35</td>
</tr>
<tr>
<td>DBP (mmHg) Mean ±SD</td>
<td>81.45±7.01</td>
<td>81.15±12.69</td>
</tr>
<tr>
<td>PR (b/min) Mean ±SD</td>
<td>75.45±7.71</td>
<td>74.95±8.85</td>
</tr>
<tr>
<td>Blood hemoglobin (g/dl)</td>
<td>1.36 ± 2.4</td>
<td>1.37 ±1.3</td>
</tr>
<tr>
<td>Fasting serum glucose mmol/l</td>
<td>3.9±1.9 mmol/l</td>
<td>11.6±6.25</td>
</tr>
<tr>
<td>Cholesterol, mmol/l</td>
<td>5.2 ± 0.2</td>
<td>5.6 ±0.2</td>
</tr>
<tr>
<td>Volume of contrast media (ml)</td>
<td>213±12</td>
<td>220±7</td>
</tr>
<tr>
<td>Triglicerides mmol/l</td>
<td>1.6 ± 0.3</td>
<td>2.3 ±0.2</td>
</tr>
<tr>
<td>Treated with ACE inhibitors, %</td>
<td>10.1</td>
<td>41.1*</td>
</tr>
<tr>
<td>Treated with diuretics, %</td>
<td>10</td>
<td>27.2 *</td>
</tr>
<tr>
<td>Atherosclerosis, %</td>
<td>40.8</td>
<td>52</td>
</tr>
<tr>
<td>Multiple coronary artery disease</td>
<td>37.2</td>
<td>66.9 **</td>
</tr>
</tbody>
</table>

*P < 0.05; **P < 0.01

BMI: body mass index ; DBP: diastolic blood pressure ; F: number of female; M: number of male

PR: pulse rate ; SBP: systolic blood pressure

2.3. Vital signs

2.3.1. **Blood pressure**: A normal blood pressure would be 120 being the systolic, over 80 the diastolic. Usually the blood pressure is read from the left arm unless there is some damage to the arm. The measurement of these pressures is done with an electronic sphygmomanometer or mercury sphygmomanometer.

2.3.2. **pulse rate**: The rate is usually measured either at the wrist or the ankle and is recorded as beats per minute. The pulse commonly taken from the radial artery at the wrist.

2.4. Clinical lab tests: The patients were examined for clinical lab tests including Hb, TG, TC, fasting serum glucose before the process of PCI, kidney function tests (serum urea and serum creatinine) were done before and after 48 hrs of PCI.

2.5. **Blood samples**: After fasting 10 hrs, ten ml of venous blood was drawn from each patient before PCI, by using sterile disposable syringes 23 G. The blood was transferred into disposable plain tube. Samples were allowed stand for 30 minutes to clot. Serum was separated by centrifugation at 3000 rpm for 5 minutes and then collected in plain tube and kept frozen until analysis. fasting blood glucose (FBG), total cholesterol (TC), triglyceride (TG), hemoglobin (Hb). And Serum creatinine, serum urea were measured before and after 48 hrs of PCI.

Coronary angiography was performed with the use of low-osmolar, non-ionic contrast agent Iohexol (Omnipaque) 844 mOsm/kg/dl. CIN was defined as a rise in serum creatinine of 0.5 mg/dL (29.7 µmol/L) or a 25% increase from the baseline values, assessed at 48 hours after the procedure.
2.6. Calculation of Glomerular Filtration Rate: Glomerular filtration rate was determined by Modification of Diet in Renal Disease (MDRD). It is likely to be more accurate as it may adjust for variations in creatinine measurements. GFR value was calculated by using age and S. Cr by using the following MDRD equation: Toprak et al., 2003.

\[
GFR \text{ (ml/min/1.73m}^2\text{)} = 186 \times (SCr^{-1.154}) \times (age^{-0.203}) \times (0.742 \text{ if female}) \times (1. 21 \text{ if black}) . \text{This equation does not require weight because the result is normalized to 1.73 m}^2\text{ body surface area which is an accepted average adult surface area.}
\]

2.7. Calculation of Creatinine Clearance: Creatinine clearance is the volume of blood plasma that is cleared of creatinine per unit time and is a useful measure for approximating the GFR. Creatinine clearance exceeds GFR due to creatinine secretion. Creatinine clearance is often measured as milliliters/minute (ml/min). The normal value of creatinine clearance in healthy adults male subjects range 97-137 ml/min and for female 88-128 ml/min. A correction factor of 0.85 for women reflects the lower muscle mass and therefore, the lower rate of creatinine production in women when compared to men Erley,1999. Creatinine clearance was calculated using Cockcroft-Gault equation : Erley,1999.

\[
Cr.Cl = [(140 - \text{age}) \times \text{Wt (kg)}) / [72 \times \text{S.Cr (mg/dl )} ] = \text{ml/min}
\]

\[
Cr.Cl (in \text{ women}) = 0.85 \times \text{Cr.Cl (in men)} = \text{ml/min}
\]

\[
Cr.Cl = \text{Creatinine Clearance, Wt = weight, S.Cr = Serum Creatinine .}
\]

In the above equation, weight should be measured in kilograms and creatinine in mg/dl Erley,1999.

2.8. Statistical Analysis:

Data were analyzed using one way Analysis of Variance (ANOVA). The mean values were compared using paired t-test. The difference between variables were considered statistically significant if (P < 0.05) and highly significant if (p<0.01). The data were expressed as mean ± standard error (SE). Analysis was conducted by using SAS program (2000).

3. Results:

3.1. Effect of Contrast Media on Serum Creatinine Level in Patients without T2DM and in Patients with T2DM after 48 hrs of PCI

Table (3-1) and Fig (3-1) show the effect of CM on serum creatinine level (µm/l) in patients without T2DM and in patients with T2DM after 48 hrs of PCI. In patients without T2DM, there was significant (p<0.05) elevation in S.Cr level by (16.3 %), from (90.1±3.6 µm/l) to (104.51±3.4 µm/l) after 48 hrs of PCI. In this group incidence of CIN was in 3 out of 22 patients. In patients with T2DM, there was significantly higher (p<0.01) increase in S.Cr level after 48hrs of PCI by (40%), from (91.1±2 µm/l) to (127.46±1.8 µm/l) after 48 hrs of PCI, in this group Incidence of CIN was 8 out of 20 patients.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Before PCI</th>
<th>After48h of PCI</th>
<th>% change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A n=22</td>
<td>90.1±3.6</td>
<td>104.51±3.4</td>
<td>+ 16. 3%</td>
</tr>
<tr>
<td>Group B n=20</td>
<td>91. 1± 2</td>
<td>127.46±1.8</td>
<td>+ 40%</td>
</tr>
</tbody>
</table>

n = number of patients.

* Significant difference compared to baseline level (P <0.05).

** Highly significant difference compared to baseline level (P <0.01).
Figure (3-1): Effect of contrast media on serum creatinine level in patients without T2DM and in patients with T2DM after 48 hrs of PCI.

n = number of patients.
* Significantly difference compared to baseline level (P <0.05).
** Highly significant difference compared to baseline level (P<0.01)

3.2. Effect of Contrast Media on Serum Urea Level in Patients without T2DM and in Patients with T2DM after 48 hrs of PCI

Table (3-2) and Figure (3-2) show the effect of CM on serum urea level (µm/l) in patients without T2DM and in patients with T2DM after 48 hrs of PCI. In patients without T2DM, there was no significant (p > 0.05) elevation in S. Urea level after 48 hrs of PCI (7.97%) increase from (4.89±1.55 µm/l) before PCI to (5.28±1.18 µm/l) after 48 hrs of PCI. In patients with T2DM, there was significant (p<0.05) elevation in S. Urea after 48 hrs of PCI (15.68%) increase from (4.91±0.87 µm/l) before PCI to (5.68 ±0.79 µm/l) after 48 hrs of PCI.

Table (3-2): Effect of Contrast Media on Serum Urea Level in Patients without T2DM and in Patients with T2DM after 48 hrs of PCI

<table>
<thead>
<tr>
<th>Groups</th>
<th>Before PCI</th>
<th>After 48 hrs of PCI</th>
<th>% change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A n=22</td>
<td>4.89±1.55</td>
<td>5.28 ±1.18</td>
<td>+7.97%</td>
</tr>
<tr>
<td>Group B n=20</td>
<td>4.91±0.87</td>
<td>5.68 ±0.79 * #</td>
<td>+ 15.68%</td>
</tr>
</tbody>
</table>

n = number of patients.
* Significantly different compared to baseline level (P <0.05).
#Significantly different between groups (P<0.05).

Figure (3-2): Effect of contrast media on serum urea level in patients without T2DM and in patients with T2DM after 48 hrs of PCI.

n = number of patients.
* Significantly different compared to baseline level (P <0.05).
3.3. Effect of Contrast Media on Glomerular Filtration Rate in Patients without T2DM and in Patients with T2DM after 48 hrs of PCI

Table (3-3) and Figure (3-3) show the effect of CM on glomerular filtration rate (ml/min/1.73m²) in patients without T2DM and in patients with T2DM after 48 hrs of PCI. In patients without T2DM, there was significant (p < 0.05) decrease in GFR level after 48hrs of PCI (14.68%) decrease from (81.7±3.1 ml/min/1.73m²) before PCI to ( 69.7±2.8 ml/min/1.73m² ) after 48 hrs of PCI. In patients with T2DM, there was significantly higher (p < 0.01) decrease in GFR level after 48hrs of PCI (21.98 %) decrease from (78.7ml/min/1.73m²) before PCI to (61.4±1.6 ml/min/1.73m²) after 48 hrs of PCI.

Table (3-3): Effect of Contrast Media on Glomerular Filtration rate in Patients without T2DM and in Patients with T2DM after 48 hrs of PCI

<table>
<thead>
<tr>
<th>Groups</th>
<th>Before PCI</th>
<th>After 48 hrs of PCI</th>
<th>% change</th>
</tr>
</thead>
<tbody>
<tr>
<td>GroupA</td>
<td>81.7±3.1</td>
<td>69.7±2.8*</td>
<td>-14.7%</td>
</tr>
<tr>
<td>GroupB</td>
<td>78.7</td>
<td>61.4±1.6 **</td>
<td>-21.98%</td>
</tr>
</tbody>
</table>

n = number of patients.
* Significantly different compared to baseline level (P <0.05).
** Highly Significant difference compared to baseline level (P <0.01).

Figure (3-3): Effect of contrast media on glomerular filtration rate in patients without T2DM and in patients with T2DM after 48 hrs of PCI

n = number of patients.
* Significantly different compared to baseline level (P <0.05).
** Highly significant difference compared to baseline level (P <0.01).

3.4. Effect of Contrast Media on Creatinine Clearance in Patients without T2DM and in Patients with T2DM after 48 hrs of PCI

Table (3-4) and Figure (3-4) show the effect of CM on Creatinine clearance (ml/min) in patients without T2DM and in patients with T2DM after 48 hrs. of PCI. In patients without T2DM, there was no significant (p > 0.05) decrease in Cr.Cl level after 48 hrs of PCI (9.16%) decrease from (101.32± 36.91 ml /min) before PCI to (92.03 ±22.2 ml/min) after 48hrs of PCI. In patients with T2DM, there was significant (p <0.05) decrease in Cr.Cl level after 48 hrs of PCI (16.44%) decrease from (122.02±35.21/min) before PCI to (101.95±25.05 ml/min) after 48 hrs of PCI.
Table (3-4): Effect of Contrast Media on Creatinine Clearance in Patients without T2DM and in Patients with T2DM after 48 hrs of PCI

<table>
<thead>
<tr>
<th>Groups</th>
<th>Before PCI</th>
<th>After 48 hrs of PCI</th>
<th>% change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>n=22</td>
<td>101.32± 36.91</td>
<td>92.03±22.2</td>
</tr>
<tr>
<td>Group B</td>
<td>n=20</td>
<td>122.02±35.21</td>
<td>101.95±25.05*#</td>
</tr>
</tbody>
</table>

n = number of patients.
* Significantly different compared to baseline level (P <0.05)
#Significantly different between groups  (P<0.05).

Figure (3-4): Effect of contrast media on creatinine clearance ml/min in patients without T2DM and in patients with T2DM after 48 hrs of PCI

n = number of patients .
 * Significantly different compared to baseline level (P <0.05).

4. Discussion:

Data obtained from the present study demonstrated high frequency of CIN development in patients with T2DM during PCI, who had more significant decrease of GFR in comparison with non diabetic patients of the same age and comparable status of renal functions (Levey et al., 2008 ; Cockcroft and Gault, 1976 ; Toprak et al., 2006).

In our study patients with T2DM, had the profile similar to the control group, proving diabetes as an independent factor contributing to CIN development (Toprak et al., 2006).

All available data obtained from the studies of effect of ACE inhibitors and blockers of angiotensin II receptors, which are widely used for treatment of patients with cardiac and renal disorders on CIN development are very contradictory (Hashemi, 2005). Treatment with diuretics in peri procedural period was also a predictor of CIN development in patients T2DM (Toprak et al., 2003 ; Erley, 1999). Intensity and extent of coronary atherosclerosis are also related to CIN development. When 2 or more coronary vessels are affected, a greater dose of contrast agent may be needed to provide more optimal visualization. A large-scale study of 5500 patients undergoing PCI demonstrated that multiple coronary artery disease is considered to be a predictor of CIN development (Mehran et al., 2004).

All patients involved in our study were given low osmolar contrast agent Omnipaque (Iohexol) which proved to be sufficiently safe. But even low-osmolar and iso-osmolar contrast agents increase the risk of CIN development with every additional 100 ml due to its dose-related effect (Bartholomew et al., 2004 ; Gruberg et al., 2001). this study has confirmed the contribution of this factor in increase of CIN development. That is why low and iso-osmolar contrast media should be used in lowest effective doses in order to increase procedure’s safety .this study demonstrated
that patient’s low baseline hemoglobin level and low hematocrit were independent predictors of increase of CIN development in patients with T2DM.

4.1. Effect of Contrast Media on Serum Creatinine Level in Patients without T2DM and in Patients with T2DM after 48 hrs of PCI

Results in table (3-1) showed that there is a significant increase in serum creatinine level in patients without T2DM after 48 hours of intravascular injection of CM, the percentage of change was (16.3 %) in this group and incidence of CIN was in 3 of 22 patients, while in diabetic patients percent of change in S. creatinine was 40 %, and incidence of CIN was in 8 of 20 patient. The result of the present study in non diabetic group is similar to the result of other study (Bartholomew et al., 2004; Gruberg et al., 2001).

In diabetic patients, there was statistically significant increase in serum creatinine level after 48hrs of PCI by 40% , the incidence of CIN was in 8 of 20 patients. This results agree with (Gruberg et al., 2001) study and (Gussenhoven et al., 1991) study. Patients with T2DM develop complications (CIN) 3 times more often, than in non-diabetic patients. This result agree with that obtained by Rudnick and Goldfarb, 2003.

4.2. Effect of Contrast Media on Serum Urea Level in Patients without T2DM and in patients with T2DM after 48 hrs of PCI

There is no significant elevation in S.urea level in patients without T2DM and there is significant elevation in S. urea level in patients with T2DM after 48hrs of PCI as compared with baseline level before PCI, although their levels are still within the normal range, the CM in diabetic patients have significant effect on S.urea compared with its effect on non-diabetic patients (Caldicott et al., 1970; Katzberg et al., 1977) . However this occurs due to the same reason which lead to increase S.Cr in diabetic patients due to hypovolemia connected to use of diuretics, beside that urea is normal metabolic waste products that were excreted by the kidneys. Urea is a byproduct of protein breakdown. In kidney disease, urea (as well as numerous others) are not excreted normally, and so they accumulate in the body thus causing an increase in blood levels of urea. As in case of dehydration or hypovolemia that is occur from the effect of CM that result from combination of direct toxicity to the renal tubular epithelium, oxidative stress, ischemic injury, and renal tubular obstruction , this results may be similar to other study where instead that blood urea increased in case of Hypovolemia, Kidney disease including glomerulonephritis, pyelonephritis, and acute tubular necrosis (Clarkson et al., 2008 ; Erley, 1999).

4.3. Effect of Contrast Media on Glomular Filtration Rate in Patients without T2DM and in Patients with T2DM after 48 hrs of PCI

GFR is important parameter to assess the renal function. It is considered to be a more appropriate index of kidney function and can be estimated from the serum creatinine (Clarkson et al., 2008). GFR is statically significantly decreased in patients with diabetes after PCI compared with the nondiabetic control group at p<0.01. Risk significantly increases in patients with T2DM and decreased GFR in the range of 3rd–4th stages of chronic kidney disease classification (Kidney Disease Outcomes Quality Initiative, 2002). In this case the frequency of CIN varies from 10% to 80%, whereas the frequency of CIN development in non diabetic patients having the same GFR value varies from 10% to 50% Rich and Crecelius, 1990 .These data demonstrate an independent contribution of diabetes to the increased risk of CIN development versus the common population.
4.4. Effect of Contrast Media on Creatinine Clearance in Patients without T2DM and in Patients with T2DM after 48 hrs of PCI

Cr.Cl can be measured from serum creatinine and creatinine excretion. The results of these tests are important in assessing the excretory function of the kidneys. Cockcroft-Gault formula used to estimate creatinine clearance (Pannu and Tonelli, 2006; Murphy, 2000) and each 10 ml/min decrease lead to increase risk by 2.7 score. Data in table (3-4) reveal that there is a significant decrease in Cr.Cl in diabetic patients as compared with non diabetic patients that is related to increase in S.Cr because it is inversely proportional to S.Cr.

4.2. Conclusions:
1. Contrast media caused more significant increase in serum creatinine level in patients with type 2 diabetes mellitus than in patients without type 2 diabetes mellitus. Moreover, the incidence of contrast induced nephropathy in diabetic patients developed three times more often than in non-diabetic patients.
2. Contrast media caused a significant increase in serum urea in patients with type 2 diabetes mellitus, whereas in patients without type 2 diabetes mellitus, serum urea did not significantly changed.
3. Contrast media caused more significant decrease in glomerular filtration rate in patients with type 2 diabetes mellitus than in patients without type 2 diabetes mellitus.
4. Contrast media caused a significant decrease in creatinine clearance level in patients with type 2 diabetes mellitus, while in patients without type 2 diabetes mellitus, creatinine clearance did not significantly changed.

Thus according to the above finding, it was concluded that diabetic patients are susceptible to higher risk of contrast induced nephropathy than non-diabetic patients.

4.3. Recommendations:
To provide a better prognosis for T2DM patients during PCI the followings are recommended to be done:
1. Evaluation of individual risk of contrast media, highest possible glucose control of carbohydrate metabolism, correction of anemia and hemodynamic disorders should be performed before the procedure.
2. Potentially nephrotoxic medications, diuretics (if possible) and metformin should be withdrawn 48 hrs before, during and 48 hrs after the procedure.
3. Iso and low osmolar agents in the lowest effective dose should be used.
4. Optimal hydration should be performed. Control of serum creatinine level 48 hrs after the procedure is obligatory.

4.4. Future Studies:
Our results can open new suggestions for future studies:
1. Study the effect of CIN in patients with chronic kidney disease.
2. Prevention of CIN with volume expansion.
3. Prevention of CIN by oral acetyl cysteine as an adjunct to saline hydration following PCI.

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