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The Relation between Pre-Procedural Increase in Urinary Albumin Excretion and Changes in Estimated Glomerular Filtration Rate after Coronary Angiography in Diabetic Patients

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ABSTRACT

Background: Contrast-induced nephropathy (CIN), is an acute impairment in renal function, and typically occurs within 3 days following the exposure to a iodinated contrast medium (CM). It is associated with increased hospital stay and increased morbidity and mortality. Adult patients with diabetes have a higher risk than the general population for developing contrast-induced nephropathy.

Objective: To assess the significance of preprocedural microalbuminuria on renal function changes post coronary angiography.

Patients and methods: The current study included 40 patients all over the age of 18 years, with diabetes mellitus type 1 or type 2, scheduled for coronary angiography with estimated GFR > 60 ml/min.

Results: incidence of contrast-induced nephropathy in this study was 40 % (n=16) of patients while 60% (n = 24) did not fit the definition of CIN. There was no statistically significant difference in the age, gender distribution and use of angiotension converting enzyme inhibitors (ACEIs) or diuretics between the cases who developed and who did not develop CIN. The mean albumin creatinine ratio (ACR) in the group with no contrast induced nephropathy was 225.38 ± 209.53 which was statistically significantly lower when compared to the cases with contrast-induced nephropathy (420.43 ± 348.52) (p = 0.033). The mean HbA1c in no contrast-induced nephropathy group was 7.11 ± 0.64 and in contrast induced nephropathy group it was 9.09 ± 0.66, which was significantly higher (P > 0.001). With univariate regression analysis, ACR, HbA1c and number of vessels affected were shown to be risk factors for occurrence of CIN after use of contrast, but with multivariate analysis, both ACR and HbA1c were shown to be risk factors for CIN.

Conclusion: An increase in urinary albumin creatinine ratio in itself maybe be a risk factor for development of contrast-induced nephropathy in diabetic patients.

Keywords: Urinary albumin excretion, Estimated glomerular filtration rate, Coronary angiography, Diabetic patients.

INTRODUCTION

Contrast-induced nephropathy (CIN) is an increasingly common cause of iatrogenic acute kidney injury (AKI) [(1)] and represents about 12% of the cases of hospital-acquired AKI [(2)]. Although the risk of renal function impairment associated with radiological procedures is low (0.6–2.3%) in the general population patients with cardiovascular disease are more susceptible, with the higher incidence being reported after emergency PCI [(3, 4)].

Although the pathophysiology of CIN is poorly understood, intrarenal vasoconstriction, and direct tubular damage are among the predominant factors contributing in the development of CIN [(5)]. Several groups have documented immediate vasoconstriction and reduction in renal blood flow occurring after administration of contrast medium [(6)]. Exposure of renal tissue to high osmotic radiocontrast agents results in characteristic histopathologic changes called "osmotic nephrosis." [(7)]. Histopathologic features of "osmotic nephrosis" includes focal or diffuse vacuolization of the proximal tubular cells as well as tubular necrosis [(8)]. Risk factors for developing CIN include diabetes with chronic kidney disease (CKD) [(5, 9)]. The overall incidence of CIN in patients with type 2 diabetes was 21.5% in a study by **Sany *et al.*** [(10)] that included 200 patients [(10)]. Evidence suggests that patients in a pre-diabetic state are also at increased risk of CIN especially if they have CKD. **Toprak *et al.*** [(11)] showed that CIN occurred in 20% of patients with CKD and diabetes and in 11.4% of patients with CKD and pre-diabetes, versus 5.5% of patients with CKD but no evidence of diabetes or prediabetes. These findings about the incidence of CIN in diabetic patients are inconsistent which might be due to the existence of different phenotypes of diabetic nephropathy [(12)].

An increase in serum creatinine and, less commonly, oliguria are the major clinical manifestations of contrast nephropathy. In a prospective study, among approximately 40 patients who developed contrast nephropathy, none was oliguric [(13)]. The increased creatinine is generally observed within 24 to 48 hours after contrast exposure and is mild. Creatinine usually starts to decline within three to seven days. Oliguria (if it occurs) occurs immediately after the procedure [(13)]. Other manifestations of acute kidney injury may be present, including hyperkalemia, acidosis and hyperphosphatemia [(14)]. The diagnosis of contrast-induced nephropathy is based upon the clinical presentation, including the characteristic rise in serum creatinine concentration beginning with the first 24 to

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48 hours after contrast exposure, and the exclusion of other causes of acute kidney injury [15].

The aime of present work was to assess the significance of preprocedural microalbuminuria on renal function changes post coronary angiography.

PATIENTS AND METHODS

This prospective study included 40 patients. The study was conducted in Ain Shams University Hospital on patients scheduled for coronary angiography. All patients had an estimated GFR preprocedure over 60 ml/min calculated by Modification of Diet in Renal Disease (MDRD) formula and all patients were diabetic (either type 1 or type 2). Patients with primary nephropathies proven by biopsies were excluded. Patients with GFR < 60 ml/min, thyroid disease or allergy to iodinated contrast were excluded from this study. All patients wee subjected to history taking as regards their antidiabetic and other antihypertensive or antiischemic medications. Serum samples for creatinine levels were measured preprocedure (day 0), day +2 and +3. Urinary albumin creatinine ration was measured using early morning urine sample preprocedure. GFR was estimated for all patients using MDRD formula (modification of diet in renal disease).

The patients were divided according to their pre-procedural urinary albumin creatinine ratio (ACR) results into 3 groups. Group 1 included patients with pre-procedure urinary albumin creatinine ratio < 30 mg/g. Group 2 included patients with pre-procedure albumin creatinine ratio 30- 300 mg/g. Group 3 included patients with pre-procedure albumin creatinine ratio > 300 mg/g. Estimated GFR (glomerular filtration rate) calculated using MDRD and serum creatinine were measured at day 2 and 3 (Day +2 and +3) after coronary angiography. Contrast-induced nephropathy was defined as rise of serum creatinine over 25% from baseline 24 to 72 hours post exposure to contrast media.

Ethical approval and written informed consent:

An approval of the study was obtained from Ain Shams University academic and ethical committee. Every patient signed an informed written consent for acceptance of the operation.

Statistical analysis

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Data were tested for normal distribution using the Shapiro Walk test. Qualitative data were represented as frequencies and relative percentages. Chi square test ($\chi 2$) to calculate difference between two or more groups of qualitative variables. Quantitative data were expressed as mean ± SD (Standard deviation). Independent samples t-test was used to compare between two independent groups of normally distributed variables (parametric data). P value < 0.05 was considered significant.

RESULTS

This study included 40 diabetic patients who underwent injection of contrast for coronary angiography. Our study population mean age was 55.42 ± 8.52 years. It included 27 males and 13 females. 65% (n = 26) of the population were hypertensive, 55% (n=22) were smokers. 57.5% (n = 23) had a BMI over 30. 19 patients were receiving metformin at time at presentation, either in combination with insulin or oral hypoglycemics.

9 patients were receiving either ACEIs or ARBs, 16 were receiving diuretics and 16 were receiving beta blockers. According to the results of urinary ACR (albumin creatinine ratio), patients were divided into 3 groups, group 1 (n = 7) with urinary ACR < 30 mg/g, group 2 (n = 19) with urinary ACR results from 30-300 mg/g and group 3 (n = 14) with urinary ACR over 300 mg/g (Table 1).

Table (1): Study population demographics and clinical data

Age (years)	Min	Max	Mean	SD
	40	76	55.42	8.5
Sex				
Males		**27**	**67.50%**	
Females		**13**	**32.50%**	
Clinical data				
HTN		**26**	**65%**	
Smoking		**22**	**55%**	
Obesity		**23**	**57.50%**	
ACR grade (mg/g)				
Grade 1 (below 30)		**7**	**17.50%**	
Grade II (30-300)		**19**	**47.50%**	
Grade III (≥300)		**14**	**35%**	

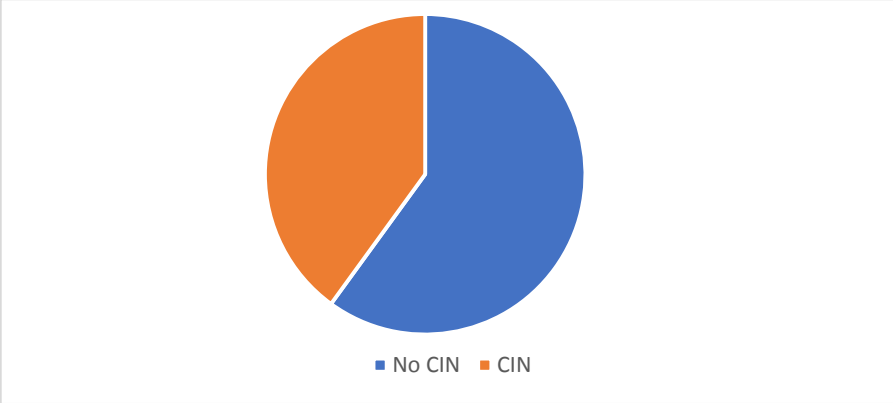

Fig (1): Pie chart for incidence of contrast-induced nephropathy in our study

40% (n = 16) of patients developed contrast-induced nephropathy post coronary angiography while 60% (n = 24) did not fit the definition of CIN (Figure 1).

Table (2): The relation between demographics and patients characteristics and the occurrence of CIN.

	No contrast induced nephropathy (N=26)	Contrast induced nephropathy (N=14)	Test of significance	P value
Age (years)	59.92 ± 7.91	54.5 ± 9.81	t= 0.499	0.621
Sex				
Males	17 (65.4%)	10 (71.4%)	$\chi 2$= 0.151	0.697
Females	9 (34.6%)	4 (28.6%)		
HTN	17 (65.4%)	9 (64.3%)	$\chi 2$= 0.005	0.945
Smoking	14 (53.8%)	8 (57.1%)	$\chi 2$= 0.041	0.842
Obesity	16 (61.5%)	7 (50%)	$\chi 2$= 0.496	0.481

Table (2) showed that the mean age of the cases with no contrast-induced nephropathy was 59.92 ± 7.91 and there were 17 males (65.4%) and 9 females (34.6%) in this group while the mean age in the group with contrast-induced nephropathy was 54.5 ± 9.81 years and there were 10 males (71.4%) and 4 females (28.6%) in this group. There was no statistically significant difference in the age and sex distribution between the cases in the two groups. Regarding the associated chronic disease in the two study groups, there were 17 cases (65.4%) and 9 cases (64.3%) with HTN in group A and group B respectively. There were 14 (53.8%) and 8 smokers (57.1%) in group A and group B respectively. There were 16 obese patients (61.5%) and 7 obese patients (50%) in group A and group B respectively. There was no statistically significant difference between the two study groups. Although more patients using metformin and ACEIs had CIN, there was no statistically significant difference within the two groups regarding the use of different drugs (Tables 3 & 4).

Table (3): Relation between HbA1C and incidence of CIN

	No contrast induced nephropathy (N=26)	Contrast induced nephropathy (N=14)	Test of significance	P value
HbA1c (%)	7.11 ± 0.64	9.09 ± 0.66	t= -9.273	< 0.001*

Table (4): The effect of patients' medication on development of CIN.

Drugs	No contrast induced nephropathy (N=26)	Contrast induced nephropathy (N=14)	Test of significance	P value
Metformin	11 (42.3%)	8 (57.1%)	$\chi2$= 0.803	0.370
ACEIs	3 (11.5%)	3 (21.4%)	$\chi2$= 0.698	0.403
ARBs	2 (7.7%)	1 (7.1%)	$\chi2$= 0.004	0.950
Diuretic	11 (42.3%)	5 (35.7%)	$\chi2$= 0.165	0.658
CCBs	5 (19.2%)	2 (14.3%)	$\chi2$= 0.154	0.695
BBs	9 (34.6%)	6 (42.9%)	$\chi2$= 0.264	0.608

In the group with contrast-induced nephropathy, out of 14 patients only 3 patients had no significant stenosis in their vessels while 6 patients had 1 vessel affected and 5 patients had 2 vessels affected. In the no contrast-induced nephropathy group, single vessel affection was present in 53.8% (n =14) of the cases and 2 vessels affection were detected in 15.4% of the cases (n=4). There was a statistically significant higher number of patients in the CIN group who had multi vessel affection (35.7%) when compared to those in the non-CIN group (15.4%).

Table (5): The relation between numbers of coronary vessels affected in coronary angiography and the development of CIN.

	Groups		Test of significance
	No contrast induced nephropathy (N=26)	Contrast induced nephropathy (N=14)	
Vessel state			
No vessels affected	8 (30.8%)	3 (21.4%)	$\chi2$= 2.211 P = 0.396
Single vessel affected	14 (53.8%)	6 (42.9%)	$\chi2$= 2.107 P = 0.432
2 vessels affected	4 (15.4%)	5 (35.7%)	$\chi2$= 4.664 P = 0.031*

The mean ACR in the group with no contrast-induced nephropathy was 225.38 ± 209.53, which was statistically significantly lower as compared to the cases with contrast-induced nephropathy (420.43 ± 348.52). Patients with grade 3 proteinuria (uACR > 300 mg) had higher incidence of contrast-induced nephropathy when compared to patients with grade 1 and grade 2 proteinuria (Table 6).

Table (6): Association between grade of proteinuria and the development of CIN.

	No contrast induced nephropathy	**Contrast induced nephropathy**	**Chi square test**	**P value**
Grade 1 (uACR 30 mg/g)	5 (19.2%)	2 (14.3%)	1.43	0.237
Grade 2 (uACR 30-300mg/g)	15 (57.5%)	4 (28.6%)	7.736	<0.001
Grade 3 (uACR > 300mg/g)	6 (23.1%)	8 (57.1%)	9.552	<0.001

Table (7): Univariate and multivariate analysis of predictors of CIN (n=14)

Variables	**Univariate analysis**	**Multivariate analysis**		
		OR	95% CI for OR	P value
Age	0.686			
Sex	0.772			
Serum creatinine before contrast	0.113			
eGFR before contrast	0.651			
CKD grade before contrast	0.567			
ACR	< 0.001*	824	273- 2.982	043*
Vessels affected	0.021*	432	286- 1.056	132
HbA1c	0.005*	684	064- 2.455	045*
HTN (hypertension)	0.231			
Smoking	0.338			
Obesity	0.154			

With univariate regression analysis, ACR, HbA1c and number of vessels affected were shown to be risk factors for occurrence of CIN after use of contrast, but with multivariate analysis, both ACR and HbA1c were shown to be risk factors for CIN (Table 7). As shown in table (8) and figure (3), the best cutoff point of ACR to predict the occurrence of CIN was more than 160 with 78% sensitivity, 57% specificity, 58% PPV, 80% NPV and total accuracy of 62%. The AUC was 0.672 with no significant difference (p=0.076).

Table (8): Analysis of the diagnostic ability of ACR to predict the occurrence of CIN.

Variable	***ACR***
AUC	***0.672***
Cut off point	***>160***
Sensitivity	***78%***
Specificity	***57%***
PPV	***58%***
NPV	***80%***
Accuracy	***62%***
P	***0.076***

AUC: area under the curve. P: probability.significant p value (< 0.05).PPV: Positive predictive value. NPV: Negative predictive value.

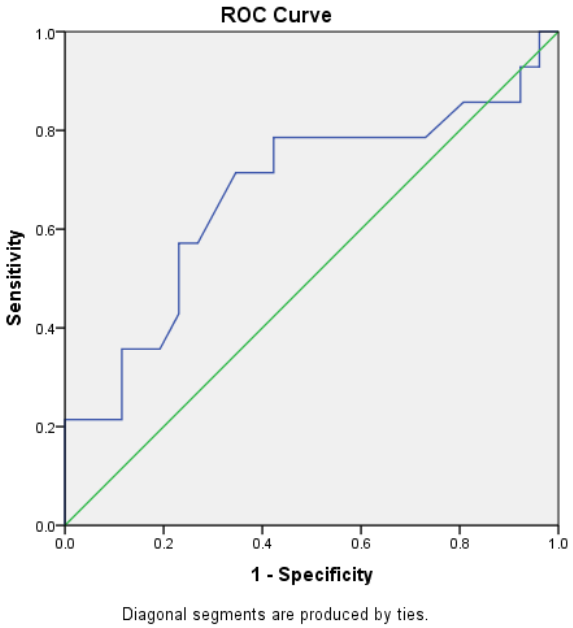

Figure (3): ROC curve for ACR to predict the occurrence of CIN.

DISCUSSION

Diabetes mellitus is a common chronic disease with high prevalence in Egypt. Contrast-induced nephropathy (CIN) is a common complication of contrast injection with diagnostic and interventional procedures such as coronary angiography. The incidence of CIN is higher among diabetic patients as compared to non-diabetics. Good control of diabetes and follow up of HbA1c can reduce the risk of CIN. Basal albumin creatinine ratio could be used as an early non-invasive marker for early prediction of CIN before its development.

Contrast-induced nephropathy (CIN), is an acute impairment in renal function, and typically occurs within 3 days following the exposure to a contrast medium (CM) [(16)]. In the United States, CIN is one of the leading causes of acute kidney injury, accounting for 11–14.5%, and is associated with increased cost, hospital stay, and long-term morbidity and mortality [(17)]**.** Patients at highest risk for CIN include those with pre-existing renal injury, particularly when it is secondary to diabetic nephropathy (DN) [(18)].

The incidence of CIN in our study was 40 %. In the study conducted by **Ma *et al.*** [(19)] the incidence of CIN was (17.78%). In one of the major epidemiological study, **Tao *et al.*** [(20)] reported 14.5% incidence of CIN after coronary intervention but those studies were not on strictly diabetic patients. Moreover, **McCullough *et al.*** [(21)] reported that the CIN rate seems to reach 50% after contrast exposure in subjects with diabetes and CKD. **Sany and his colleagues** [(10)] showed that overall incidence of CIN in type II diabetic patients was 21.5% (43 out of 200 patients), incidence of CIN in diabetic patients with microalbuminuria was 17% (17 out of 100 patients), while incidence of CIN in diabetic patients with macroalbuminuria was 26% (26 out of 100 patients**).**

It was reported that higher prevalence of CIN was observed in patients with increased age, possibly reflecting the decline in renal function with age. Advanced age is associated with increased vascular stiffness with declined endothelial function [(5)]. However, there was no difference as regards both groups regarding the age in our study. Several drugs are known to affect renal blood flow especially ACEIs and ARBs.

In this study, there was no significant association between the development of contrast-induced nephropathy and the use of different drugs including metformin, ACEIs, angiotensin II receptor blockers (ARBs), diuretics, calcium channel blockers (CCBs) and beta-blockers (BBs). This agrees with **Ma and his colleagues** [(19)] who showed that there is no statistically significant difference in the use of different drugs between the cases who developed and who didn't develop CIN except for digoxin and spironolactone, however none of the patients in this study were on either drugs .

Hyperglycemia is a well-known risk factor for endothelial dysfunction. **Basile *et al.*** [(22)] reported that microvascular damage significantly affects the kidney in short and long term. In our study, the mean HbA1c in the group that did not develop contrast-induced nephropathy was significantly lower (7.11 ± 0.64) than in the contrast-induced nephropathy group (9.09 ± 0.66) (P > 0.001). Further, poorly controlled blood sugar contributes to endothelial cell dysfunction making the effect of iodinated contrast more pronounced on the kidneys.

Isobe *et al.* [(23)] reported that after adjusting for risk factors, the multivariate logistic regression

analysis revealed that pre-procedural urinary microalbumin levels and HbA1c were independent predictors for CIN (OR: 1.030, 95% CI: 1.020–1.039, p = 0.008).

In our current study, more patients with multiple diseased vessels in their coronary angiography had contrast-induced nephropathy than those who had no or single vessel affection, which was found to be statistically significant (p= 0.031). This agrees with **Ma and his colleagues** [19] who revealed that multi-vessel coronary disease in CIN group were significantly higher than that in no CIN group (p < 0.005) [19]. Possibly due to the larger volume of contrast required in such patients to visualize diseased vessels and the worst state of blood vessels as regards atherosclerosis, which might also affect renal as well as coronary vasculature.

An Egyptian study conducted by **Sany *et al.*** [10] showed that cases who developed CIN after injection of the dye had higher base line serum creatinine (1.18 ± 0.19 vs. 1.05 ± 0.15, p < 0.001), and lower creatinine clearance (78.26 ± 22.07 vs. 92.75 ± 9.27, p < 0.001). In our study, the baseline serum creatinine was lower in the group with no contrast-induced nephropathy (1.04 ± 0.2 mg/dl) while in the contrast-induced nephropathy group, serum creatinine pre contrast was 1.12 ± 0.14 mg/dl and the estimated GFR was lower. This may be explained by the fact that all patients had GFR over 60 ml/min before contrast and that the study did not include patients with advanced CKD.

In this study, the mean urinary ACR in the group with contrast-induced nephropathy was significantly higher (420.43± 348.52 mg/g) as compared to mean urinary ACR in the group that did not develop contrast-induced nephropathy (225.38 ± 209.53 mg/g) (p = 0.033). Most patients who developed contrast-induced nephropathy had high degree of proteinuria (urinary ACR > 300 mg/g) (n = 8). This agrees with Ma ***et al.*** [19] who found that urinary ACR levels were higher in patients who developed CIN (50%) as compared to the cases with no CIN (12.84%) (P < 0.001). This also agrees with **Sany *et al.*** [10] who reported that cases who developed CIN had higher urinary ACR as compared to the cases who didn't develop CIN (583.4 ± 471.91 vs. 343.2 ± 358.8, p = 0.003). Since, the development of albuminuria is the first stage of development of diabetic nephropathy and diabetic kidney disease, the presence of albuminuria itself signifies the presence of endothelial damage even before decline of GFR, possibly making the kidneys to be more susceptible to damage by contrast material.

With univariate regression analysis of data in this study , urinary ACR, HbA1c and number of vessels affected was shown to be risk factors for occurrence of CIN after use of contrast, but with multivariate analysis, only urinary ACR and HbA1c was shown to be an independent risk factors for CIN. Other studies confirmed that pre-contrast GFR, urinary ACR [19], anemia, heart failure [23] dehydration [24] and HbA1c [25] as independent risk factors for CIN. All of the above data further signifies the additive and cumulative effects of several risk factors in the development of contrast-induced nephropathy.

CONCLUSION

We concluded that among diabetic patients even with estimated GFR over 60, increased urinary albumin creatinine ratio could be a risk factor for the development of contrast-induced nephropathy post coronary angiography. In addition, the study highlighted the importance of proper control of blood sugar and the state of blood vessel. Further studies including larger number of patients may be needed to define the role of albuminuria in contrast-induced nephropathy.

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