Study of Urine Neutrophil Gelatinase Associated Lipocalin (NGAL) in Post Percutaneous Coronary Intervention Contrast Induced Acute Kidney Injury

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Abstract: BACKGROUND: The intravascular administration of iodinated contrast media is a well-recognized cause of acute kidney injury (AKI), which in turn, is associated with in-hospital morbidity and mortality. In the absence of effective, specific therapies for AKI, the early and accurate detection of AKI is crucial to prevent its progression, and thereby, to potentially improve its outcome. The quest to improve early diagnosis of AKI is an area of intense research. **AIM:** The aim of the study was to investigate the value of estimation of urinary NGAL in the early detection of contrast induced acute kidney injury (CIAKI) after percutaneous coronary intervention (PCI). **METHODS**: The study included 43 patients; 31 males and 12 females in addition to 10 apparently healthy controls. They underwent elective PCI in Elmehala Elkobra cardiology center. Our study defined contrast induced acute kidney injury as increased serum creatinine after contrast injection more than 0.3mg/dl or 25% from the base line. Patients were subjected to full history, clinical examination with calculation of body weight and routine radiological & laboratory investigations including serum creatinine (pre PCI, 48 hours post PCI and 72 hours post PCI) with estimated glomerular filtration rate (eGFR), and urine NGAL (pre PCI and 4 hours post PCI). **RESULTS:** Thirteen out of the 43 studied patients (30.2%) developed CIAKI. There was a significant difference between CIAKI group and non-CIAKI group regarding the volume of contrast, hematocrit, blood urea, eGFR, 48 hours post PCI serum creatinine, 72 hours post PCI serum creatinine and 4 hours post PCI urine NGAL. Four hours post PCI urine NGAL was significantly higher than base line urine NGAL in CIAKI group. Four hours post PCI urine NGAL was significantly higher in proteinuric than non proteinuric patients. Four hours post PCI urine NGAL correlated significantly positive with 72 hours post PCI serum creatinine. **CONCLUSION:** A Significant rise in urine NGAL was demonstrated 4 hours after contrast administration and was significantly correlated with a rise in serum creatinine 72 hours after contrast. Thus urine NGAL can be a promising early predictive biomarker for diagnosing CIAKI. NGAL might facilitate earlier intervention to prevent CIAKI and improve outcome.

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Key words: Urine NGAL, PCI, AKI

1. Introduction

Acute kidney injury (AKI) is a common syndrome in hospitals and intensive care units **(1).** The term AKI has been proposed to encompass the entire spectrum of acute renal dysfunction from minor changes in renal functions to requirement for renal replacement therapy **(2).**

Use of intravascular contrast media (CM) is widespread and continues to expand **(3).** The intravascular administration of iodinated CM is a well-recognized cause of AKI, which in turn, is associated with in-hospital morbidity and mortality **(4).** CM was the next most common cause, accounting for 12% of cases of AKI, and was associated with an in-hospital mortality of 6% **(4).** Toxic renal tubular damage and hypoxic injury caused by CM are the leading proposed causes of contrast induced nephropathy pathogenesis **(5).**

The quest to improve early diagnosis of AKI is an area of intense research. In the absence of effective, specific therapies for AKI, the early and accurate detection of AKI is crucial to prevent its progression, and thereby, to potentially improve its outcome **(6).** Serum creatinine is the most common marker of kidney function used in clinical practice. Nonetheless, the limitations of using serum creatinine as a kidney function measure are well documented **(7).**

Neutrophile gelatinase associated lipocalin (NGAL) also known as lipocalin-2, is a member of lipocalin family that is comprised of functionally diverse but structurally conversed small proteins **(8).** NGAL has been implicated in a variety of processes including inflammation, apoptosis, and organogenesis which makes it a promising biomarker in acute renal failure **(9).** NGAL was identified as one of the most up regulated genes in the kidney

soon after ischemic injury. NGAL protein was also markedly induced in kidney tubule cells and easily detected in the plasma and urine in animal models of ischemic and nephrotoxic AKI **(10).** The expression of NGAL protein was also dramatically increased in kidney tubules of humans with ischemic, septic, and post-transplant AKI **(11).**

The genesis and sources of plasma and urine NGAL following AKI require further clarification. Although plasma NGAL is freely filtered by the glomerulus, it is largely reabsorbed in the proximal tubules by efficient megalin-dependent endocytosis. **(12).** Direct evidence for this notion is derived from systemic injection of lapelled NGAL, which becomes enriched in the proximal tubule but does not appear in the urine in animals **(13).** Thus, any urine excretion of NGAL is likely only when there is concomitant proximal renal tubular injury that precludes NGAL reabsorption. However, gene expression studies in AKI have demonstrated a rapid and massive up regulation of NGAL mRNA in the distal nephron segments – specifically in the thick ascending limb of Henle's loop and the collecting ducts **(12).** The resultant synthesis of NGAL protein in the distal nephron and secretion into the urine appears to comprise the major fraction of urine NGAL. Supporting clinical evidence is provided by the consistent finding of a high fractional excretion of NGAL reported in human AKI studies **(12).** The endogenous role of NGAL remains unclear. It seems to be involved with iron transportation to and from the proximal tubular epithelial cells, and animal studies demonstrate a Reno-protective effect of exogenously administered NGAL in the setting of acute ischemic injury **(14).**

NGAL measurement has now been commercialized and can be performed in both blood and urine samples. Both urine and blood samples have their advantages and shortcomings. Blood NGAL measurements are invasive and may potentially reflect the effect of extra-renal disease on NGAL concentrations. However samples are readily available and the measurement can be performed rapidly on whole blood or plasma (15-20 min) on a point-of-care device. Urine sampling is non-invasive and there are less potentially interfering proteins present than in blood specimens. However disadvantages include the lack of available specimen in oliguric patients, the effect of over- or under-hydration and diuretic treatment on measured urinary NGAL concentrations and a longer analytical time on a laboratory-based analyzer. This choice in sample type and platform allows the flexibility to offer the test in a variety of different clinical settings **(15).** Urine NGAL seems to be even better than plasma NGAL **(16).**

NGAL appears to be an exciting marker of AKI but more work needs to be done to confirm its utility in routine clinical practice and to fine-tune the choice of appropriate cut-offs for different clinical settings and populations.

Our aim was to study the value of estimation of urine NGAL in the early detection of renal damage in patient with contrast induced AKI after PCI.

2. Subjects and Methods:

The study included 43 patients; 31 males and 12 females with ages ranged from 43 to 64 years. They underwent elective Percutaneous Coronary Interventions (PCI) in Elmehala Elkobra cardiology center in Gharbia, Egypt. We obtained written informed consent from the legal guardian of every participant before enrollment. The protocol was approved by the local ethics committee. In addition, 10 apparently healthy age and gender matched control subjects were also included. Exclusion criteria for patients included, patients with history of myocardial infarction less than three months before the procedure, congestive heart failure, sepsis or recent history of ICU admission, end stage chronic kidney disease, malignancy, acute or chronic liver diseases, urinary tract infection assessed by history and urine analysis **(17),** history of diuretic therapy and history of nephrotoxic drugs one week before the procedure.

Patients were subjected to full medical history, complete clinical examination with calculation of body weight, routine investigations including: complete urine analysis, complete blood count (CBC), erythrocyte sedimentation rate (ESR), random blood glucose (RBG), lipid profile (total cholesterol, triglyceride), serum electrolytes (sodium & potassium), serum creatinine (pre PCI, 48 hours post PCI and 72 hours post PCI), estimated glomerular filtration rate [eGFR] by: a) Cockcroft-Gault formula; GFR = {140 – age (years)} × Lean Body weight (Kg) / Serum creatinine × 72 × [0.85 if female] (**18).** b) **M**odification of **D**iet in **R**enal **D**isease formula (MDRD); GFR (mL/min/1.73 m^2) = 175 **x** (Serum creatinine)$^{-1.154}$ x (Age)$^{-0.203}$ x (0.742 if female) x (1.212 if African American) (conventional units) **(19)**, Liver functions [ALT, AST, PT, serum albumin], resting 12 leads electrocardiography (ECG), echocardiography and urine NGAL (pre PCI and 4 hours post PCI). The volume of contrast used ranged from 50 to 400 ml.

For urine NGAL analysis, mid-stream urine samples were properly centrifuged and the supernatant was separated and freezed till analysis. The urine NGAL was performed using a commercially available assay (BioVendor Research and Diagnostic Products, The RD191102200R

Human Lipocalin-2/NGAL ELISA, USA) that specifically detects human NGAL. The assay was performed according to manufacturer's protocol. Standards, quality controls and samples are incubated in micro plate wells pre-coated with polyclonal anti-human lipocalin-2 antibody. After one hour incubation and washing, biotin labeled polyclonal anti-human lipocalin-2 antibody is added and incubated with captured lipocalin-2 for one hour. After another washing, streptavidin-HRP conjugate is added. After 30 minutes incubation and the last washing step, the remaining conjugate is allowed to react with the substrate solution (TMB). The reaction is stopped by addition of acidic solution and absorbance of the resulting yellow product is measured. The absorbance is proportional to the concentration of lipocalin-2. A standard curve is constructed by plotting absorbance values against concentrations of standards, and concentrations of unknown samples are determined using this standard curve.

Statistical Analysis:

The data collected were tabulated and analyzed by SPSS statistical package version 11 on IBM compatible computer. Quantitative data were expressed as mean & standard deviation (X±SD) and analyzed by applying ANOVA test for analysis of variance, student t-test for comparing two groups of normally distributed variables and Mann whiteny test for comparing two small groups or of abnormally distributed variables Qualitative data were expressed as number and percentage (No & %) and analyzed by applying chi-square test. Correlation co-efficient test (r-test) was used for correlation between two quantitative variables. Results were considered of significance at $P<0.05$.

3. Results:

Demographic and laboratory data of studied patients and controls are shown in table (1)

Table (1): Demographic and laboratory data of studied patients and controls.

Groups / Parameters	Patients (n=43)	Controls (n=10)	*P*-Value
	X±SD	X±SD	
Age (years)	54.95±5.78	51.4±5.78	>0.05
Sex			>0.05
Male	31	7	
Female	12	3	
Body weight	78.56±4.66	79.1±4.18	>0.05
Hb (gm/dL) Pre PCI	12.67±0.79	13.07±0.61	>0.05
Hematocrit % Pre PCI	38.47±3.3	41.6±1.89	**<0.05**
Serum cholesterol (mg/dL) Pre PCI	186.39±38.32	172.4±19.78	>0.05
Serum triglyceride (mg/dL) Pre PCI	168.39±81.03	117.2±50.79	>0.05
RBG (mg/dL) Pre PCI	161.2±84.95	95.9±6.24	**<0.05**
ALT (u/l) Pre PCI	38.09±13.69	28.2±6.41	**<0.05**
AST (u/l) Pre PCI	35.09±13.54	28.8±8.26	>0.05
Blood urea (mg/dL) Pre PCI	29.65±4.21	26.3±2.49	**<0.05**
Serum creatinine (mg/dL)			
Pre PCI	1.06±0.14	0.96±0.12	**<0.05**
48 hours post PCI	1.12±0.19	----------	
72 hours post PCI	1.24±0.29	----------	
Serum soduim (mEq/L) Pre PCI	143.3±15.7	140.6±4.48	>0.05
Serum potassuim (mEq/L) Pre PCI	4.29±0.49	4.32±0.44	>0.05
eGFR (ml/min) Pre PCI			
MDRD	86.78±8.99	94.91±3.56	**<0.05**
Cockroft	83.09±11.47	93.33±5.49	**<0.05**
Urine NGAL (ng/ml)			
Pre PCI	13.28±13.61	11.1±6.03	>0.05
4 hours post PCI	39.25±31.13	----------	

PCI = Percutaneous Coronary Interventions, RBG= random blood glucose, eGFR= estimated glomerular filtration rate, ALT= alanin transaminase, AST= aspartate transaminase,b Hb= haemoglobin. NGAL= Neutrophil-Gelatinase-Associated Lipocalin. $P<0.05$ is considered significant.

Patients' characteristics are shown in table (2): In this study, 18 patients were diabetic (41.9%), 16 patients were hypertensive (37.2%). Eleven patients showed proteinurea (25.6%). High osmolar contrast used in 38 patients and low osmolar contrast used in 5 patients. CIAKI developed in 13 patients (30.2%) while it did not develop in 30 patients (69.8%).

Table (2): Patients' characteristics and type of contrast.

Parameters	Patients (N=43)	
	N	%
DM positive	18	(41.9)
negative	25	(58.1)
Duration (years) (X±SD)	17.94±5.93	
HTN positive	16	(37.2)
negative	27	(62.8)
Duration (years) (X±SD)	9.44±7.16	
Protienurea positive	11	(25.6)
negative	32	(74.4)
High osmolar contrast	38	(88.4)
Low osmolar contrast	5	(11.6)
With CIAKI	13	(30.2)
Without CIAKI	30	(69.8)

CIAKI= contrast induced acute kidney injury, DM= diabetes mellitus, HTN= hypertension

The frequency of hypertension, diabetes plus hypertention, proteiurea, hypertention plus proteiurea and absence of risk factors, all differed significantly between patients who develop CIAKI and those who did not develop CIAKI (Table 3):

Table (3): Classification of patients with CIAKI and those without CIAKI according to risk factors and contrast type.

Patients / Risk factors	Patients				*p*-value
	With CIAKI (n=13)		Without CIAKI (n=30)		
	n =13	(%)	n =30	(%)	
DM	2	(15.38)	6	(20)	>0.05
HTN	4	(30.76)	2	(6.66)	**<0.05**
DM with HTN	7	(53.84)	3	(10)	**<0.001**
Proteinurea	8	(62.5)	3	(10)	**<0.001**
HTN with Proteinurea	8	(62.5)	2	(6.66)	**<0.001**
Without risk factor	0	(0)	19	(57.3)	**<0.001**
High Osmolar contrast	12	(92.3)	26	(86.7)	>0.05
Low Osmolar contrast	1	(7.7)	4	(13.3)	>0.05

CIAKI= contrast induced acute kidney injury, DM= diabetes mellitus, HTN= hypertension. *P*<0.05 is considered significant

Patients who developed CIAKI and those who did not develop CIAKI differed significantly according to the volume of contrast, the hematocrit, blood urea, both second and third day post PCI serum creatinine and eGFR (Table 4).

Table (4): Laboratory data of CIAKI group and non CIAKI group

Group / Parameters	Patients (n=43)		*p*-value
	CIAKI (n=13)	Non CIAKI (n=30)	
Age	56.46±5.59	54.3±5.83	>0.05
volume of contrast (ml)	160±75.76	112±68.54	**<0.05**
Hb (g/dL) Pre PCI	12.34±0.79	12.81±0.76	>0.05
Hematocrit % Pre PCI	36.54±3.55	39.3±2.87	**<0.05**
Blood urea (mg/dL) Pre PCI	32.46±4.56	28.43±3.46	**<0.001**
Serum creatinine (mg/dL)			
Pre PCI	1.12±0.15	1.03±0.13	>0.05
48 hours post PCI	1.28±0.17	1.05±0.16	**<0.001**
72 hours post PCI	1.59±0.22	1.09±0.17	**<0.001**
GFR (ml/min) Pre PCI			
MDRD	79.69±6.81	89.85±8.12	**<0.001**
Cockroft	74.87±10.01	86.45±10.27	**<0.001**

CIAKI= contrast induced acute kidney injury, PCI = Percutaneous Coronary Interventions, GFR= glomerular filtration rate, Hb= haemoglobin. *P*<0.05 considered is significant.

In both patients' groups (those with CIAKI and those without CIAKI), 4 hours post PCI urine NGAL was higher than pre PCI urine NGAL (Table 5).

Table (5): Urine NGAL level in patient with and without CIAKI

Patients / NGAL	Patients		U-test	*p*-value
	With CIAKI (n=13)	Without CIAKI (n=30)		
	X±SD	X±SD		
NGAL (ng/mL)				
Pre PCI	14.17±11.13	10.57±11.88	1.91	>0.05
4 hours post PCI	78.37±12.56	28.3±18.85	5.04	**<0.001****
Paired t-test	16.02	4.19		
p-value	**<0.001****	**<0.001****		

NGAL= Neutrophil-Gelatinase-Associated Lipocalin, CIAKI= contrast induced acute kidney injury, PCI = Percutaneous Coronary Interventions, *P*<0.05 is considered significant.

Both pre PCI urine NGAL and 4 hours post PCI urine NGAL were significantly in proteinuric than in non-proteinuric patients (Table 6).

Table (6): Urine NGAL level in proteinuric and non proteinuric patients

patients / NGAL	Proteinuric (n=11) X±SD	Non-proteinuric (n= 32) X±SD	*p*-value
NGAL (ng/ml)			
Pre PCI	33.43±12.18	8.94±6.51	**<0.001**
4 hours post PCI	71.07±25.67	28.42±24.85	**<0.001**

NGAL= Neutrophil-Gelatinase-Associated Lipocalin. PCI = Percutaneous Coronary Interventions. *P*<0.05 is considered significant.

Urine NGAL (pre PCI and 4 hours post PCI) did not differ significantly between patients who received high osmolar contrast (HOC) and those who received low osmolar contrast (LOC) in the whole patient group, in patients with CIAKI and in those without CIAKI.

Both pre PCI urine NGAL and 4 hours post PCI urine NGAL were significantly positively correlated with the volume of contrast, blood urea and both second and third day post PCI serum creatinine. They were significantly negatively correlated with HB, Hematocrit and eGFR. Four post PCI urine NGAL was significantly positively correlated with the duration of the procedure (Table7).

Table (7): Pearson correlations between urine NGAL (pre PCI & post PCI) and laboratory parameters.

Group / parameters	All patients (n=43)			
	Pre PCI urine NGAL		Post PCI urine NGAL	
	r	p-value	r	*p*-value
Volume of contrast (ml)	-	-	0.53	**<0.001**
Duration of procedure (minute)	-	-	0.83	**<0.001**
Hb (g/dL) Pre PCI	-0.65	**<0.001**	-	-
Hematocrit % Pre PCI	-0.75	**<0.001**	-	-
Blood urea (mg/dL) Pre PCI	0.73	**<0.001**	0.66	**<0.001**
Serum creatinine (mg/dL)				
Pre PCI	0.65	**<0.001**	0.51	**<0.001**
48 hours post PCI	0.65	**<0.001**	0.76	**<0.001**
72 hours post PCI	0.67	**<0.001**	0.88	**<0.001**
eGFR (ml/min), Pre PCI				
MDRD	-0.64	**<0.001**	-0.68	**<0.001**
Cockroft	-0.69	**<0.001**	-0.59	**<0.001**

NGAL = Neutrophil-Gelatinase-Associated Lipocalin
PCI = Percutaneous Coronary Interventions
Hb= haemoglobin, *P*<0.05 is considered significant.

Cut off level for 4 hours post PCI urine NGAL at which CIAKI develop, was (51.5 ng/ml) with sensitivity of 100%, specificity of 90%, positive prediction value (PPV) of 81%, negative prediction value (NPV) of 100% and accuracy of 93 % (Figure1).

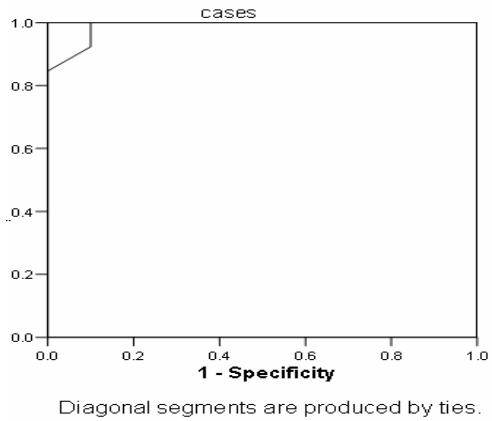

Figure (1): Receiver Operating Characteristic (ROC) curve showing the cut off level for urine NGAL at which there is increase in post PCI serum creatinine by >0.3mg/dl.

4.Discussion

Since the early stages of AKI are often reversible, AKI should be prevented and/or treated by various approaches instituted as early as possible after the initiating insult, well before serum creatinine even begins to rise. The rise in serum creatinine is slow following the onset of AKI. By the time a change is observed in serum creatinine, a critical 'window of therapeutic opportunity' may have already been missed **(20).**

Contrast-induced AKI has serious prognostic implications; it is linked to increases in length of hospital stay and to higher rates of in-hospital cardiovascular events, in-hospital mortality, and 1-year and 5-year mortality rates. Even relatively small changes in renal function after administration of contrast medium are associated with substantial increases in mortality rates; this finding suggests that renal insufficiency is a sensitive marker of poor outcomes for patients at risk or perhaps that transient episodes of renal ischemia may produce secondary hemodynamic or vascular changes in other organs **(21).**

Serum creatinine, although used routinely in clinical practice, may be an unsatisfactory marker of acute renal dysfunction. An increase of serum creatinine is more related to loss of the filtration function but not to acute tubular injury. There is a delay in the detectable increase of the serum creatinine level, so it cannot be a reliable early biomarker for AKI **(22)**

NGAL is expressed at very low levels in the kidney. It is markedly increased in stimulated epithelia, and it is also one of the maximally expressed genes in the kidney after early ischemic injury **(23).**

In our study we investigated urine NGAL as an early marker for detection of contrast induced acute kidney injury; we measured urine NGAL level before contrast administration and 4hours after the procedure. Our study defined contrast induced acute kidney injury as increased serum creatinine after contrast injection more than 0.3mg/dl or 25% from the base line and this goes with definition of CIAKI by **McCullough (24).**

In our study 9/18 diabetic patients developed CIAKI (representing 69% of CIAKI patients). This agreed with **Malyszko *et al.* (25)** who concluded that diabetic patients are more vulnerable and prone to develop contrast nephropathy. Eight out of eleven patients with chronic kidney disease evidenced by proteinurea developed CIAKI (representing 61.5% of CIAKI patients). **Toprak (26)** reported that the most important and well-established patient-related risk factors for CIAKI are chronic kidney disease (CKD); particularly CKD combined with diabetes mellitus and advanced age. **Morabito *et al.* (27)** concluded that the incidence of CIAKI after PCI was higher in patients with CKD associated with diabetes.

Comparing patients who developed CIAKI and those who did not develop CIAKI, we found that the volume of contrast was significantly higher in those who developed CIAKI. This agreed with **Morabito *et al.* (27)** who concluded that contrast media volume, especially if exceeding the dose adjusted for renal function, was a strong modifiable risk factor for CIAKI. This was also in agreement with **Sanaei-Ardekani *et al.* (28)** who reviewed 931 cases of coronary angiography and found increased CIAKI with increased volume of contrast. Hematocrit was significantly lower in patients who developed CIAKI group. This result was in concordance with **Cho *et al.* (29)** who studied effect of contrast-induced nephropathy on cardiac outcomes after use of nonionic iso-osmolar contrast media during coronary procedure and found that patients who developed CIAKI had lower baseline hematocrit level compared to those who did not develop CIAKI. There was no significant difference between the two groups regarding to haemoglobin. In contrary, **Morabito *et al.* (27)** reported that lower levels of basal hemoglobin appeared to be related to a higher risk of CIAKI. Base line eGFR calculated by either MDRD or Cockroft formula was significantly lower in patients who developed CIAKI. This was in line with **Ling *et al.* (30).** Base line serum creatinine and base line urine NGAL did not differ significantly between the two groups. Second and third day post contrast serum creatinine in addition to 4 hours post contrast urine NGAL were all significantly higher in patients who developed CIAKI than those who did not develop CIAKI. This also agreed with **Ling *et al.***

(30) study. Elevated 4 hours post contrast urine NGAL in patients who developed CIAKI was also going with what was found in **Malyszko *et al.* (25)** study.

In both patients with CIAKI and those without CIAKI, 4 hours post contrast urine NGAL was significantly higher than base line urine NGAL. This was going with **Ling *et al.* (30)** and **Malyszko *et al.* and (25)** studies regarding patients who developed CIAKI **and with Bachorzewska *et al.* (31), Ling *et al.* (30), Bachorzewska *et al.* (32) and Malyszko *et al.* (25)** studies regarding patients who did not develop CIAKI.

Both pre PCI urine NGAL and post PCI urine NGAL were significantly higher in proteinuric than non proteinuric patients which was agreed with **Bolignano *et al.* (33)**.

Analyzing the type of contrast agent, our study found no significant difference between low osmolar (n=5) and high osmolar contrast (n=38) with regards to 4 hours post contrast urine NGAL. This result was agreed with **Bachorzewska *et al.* (30)**.

Correlating urine NGAL; both base line and 4 hours post contrast with clinicopathological patients' profile revealed that:

a) Base line urine NGAL correlated significantly positive with base line serum creatinine and urea which was agreed with **Bachorzewska *et al.* (30) and Yang *et al.* (33).** It was significantly negatively correlated with both haemoglobin concentration and haematocrit which was similar to what was reported by **Malyszko *et al.* (35).** It was also significantly negatively correlated with eGFR which was in concordance with both **Yang *et al.* (34) and Bolignano *et al.* (36)**.

Mori and Nakao (37) proposed an interesting theory which might explain the relationship between NGAL and GFR, suggesting that the increase in NGAL is not just the passive consequence of a reduced renal clearance. This hypothesis, called the "forest fire theory," assumes that the increase in NGAL in chronic kidney disease ("forest fire") is the consequence of a sustained production by "inflamed" but vital tubular cells, whereas the rise in serum creatinine and the contraction of GFR are the mere passive result of a general loss of functional cells or nephrons. From this point of view, NGAL would represent a real-time indicator of how much active kidney damage exists within the overall condition of chronic renal impairment.

b) Four hours post contrast urine NGAL was significantly positively correlated with the volume of contrast. This was in contrast to what was reported in **Bachorzewska *et al.* (31)** study**.** Their patients were on statins and angiotensin converting enzyme inhibitors but our patients were not. **Wagener *et al.* (38)**, showed that urine NGAL appears to be significantly influenced by medications, and found that all patients who received aprotinin experienced marked elevations in urine NGAL, while patients who received eminocaproic acid experienced minimal elevations which might explain our results. Four hours post contrast urine NGAL was significantly positively correlated with the time of the procedure. A similar correlation was also reported by **Mishra *et al.* (39) and Bachorzewska *et al.* (31).** It also correlated significantly positive with post contrast serum creatinine which was agreed by both **Yang *et al.* (34) and Bolignano *et al.* (36)**.

In the current study the 4 hours post PCI urine NGAL cut off level for the development of CIAKI was 51.5 ng/ml; at which serum creatinine increased by 0.3 mg/dl. It detected CIAKI with sensitivity of 100% and specificity of 90%. This result was in agreement with that reported by **Makris *et al.* (40)** who studied the role of urine NGAL to urine creatinine ratio in the early detection of CIAKI after coronary artery angiography and reported urine NGAL cut off level 52.5 ng/ml with the same sensitivity and specificity. This was different from what reported by **Hirsch *et al.* (41)** in their study of NGAL as an early predictive biomarker of contrast-induced nephropathy in children. They determined urine NGAL cut off level 100 ng/ml for 2 hours post PCI with sensitivity of 73% and specificity of 100% and for 6 hours post PCI with sensitivity of 90% and specificity of 99%.

Conclusion:

A Significant rise in urine NGAL was demonstrated 4 hours after contrast administration and was significantly correlated with the rise in serum creatinine 72 hours after contrast. Thus estimation of urine NGAL can be a promising early predictive biomarker for diagnosing of CIAKI. NGAL might facilitate earlier intervention to prevent contrast induced acute kidney injury and improve outcome. Urine NGAL > 51.5 ng/ml can be used as useful predictor for the occurrence of contrast induced acute kidney injury.

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