Kidney injury molecule-1: a urinary biomarker for contrast induced acute kidney injury.

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ABSTRACT

Back ground: Urinary kidney injury molecule 1 (KIM-1) is early biomarker for renal damage. A few studies have been published analyzing the potential use of urinary kidney injury molecule-1 (KIM-1) as a biomarker for acute kidney injury. However no study has been done related to Acute Kidney Injury associated with contrast administration.

Aim: To search for new markers to identify Acute Kidney Injury (ARF) associated with contrast administration earlier than serum creatinine.

Material and Methods: We studied 100 consecutive patients with normal serum creatinine undergoing angiographic procedure. We assessed urine KIM-1, at 4h, 8h, and 24 hours after the angiographic procedure. Serum creatinine was measured at basal, 24h and 48 hours after the procedure.

Results: There was a significant rise in urinary KIM-1 levels at 24 hours after the angiographic procedure. The presence of contrast induced nephropathy associated with acute Kidney Injury was 12%.

Conclusion: The present study highlighted the importance of urinary KIM-1 in detecting Acute Kidney Injury associated with contrast administration earlier than Serum creatinine.

Key words: Neutrophil-gelatinase-associated lipocalin. Contrast-induced nephropathy. Cystatin C. Glomerular Filtration Rate (GFR), Kidney injury molecule -1 (KIM-1).

INTRODUCTION

The requirement for radiological investigations using contrast media has increased. Contrast induced nephropathy is emerging a significant source of hospital morbidity and mortality with the ever increasing use of iodinated contrast media in diagnostic imaging and interventional procedures such as angiography. The rate of incidence of contrast-induced nephropathy as a complication of radiographic diagnostic and interventional studies varies markedly, depending on the definition used and on other variables such as the type of radiology procedure performed, the dose and type of contrast agent administered, the differing patient populations in regard to number and type of risk factors, and the length of patient follow-up renal function deterioration according to most authors is referred to an increase of serum creatinine concentration of >0.5 mg/dl or 25% above baseline, within 48 hours after contrast medium administration. Contrast induced nephropathy is most commonly defined as Acute Kidney Injury occurring within 48 hours of exposure to intravascular radiographic contrast material that is not attributable to other causes[1]. Contrast induced acute kidney injury (CIAKI) has subsequently become the third most common reason for the development of in-hospital acute kidney injury accounting for 12% of cases[2]. This iatrogenic complication has been a subject of concern in recent years because of its adverse effects on prognosis and addition to health care costs. The exact underlying mechanisms of nephrotoxicity have yet to be fully elucidated but are likely to involve the interplay of several pathogenic factors.

Several studies revealed that contrast medium can cause kidney damage and even cell death. Moreover, contrast medium can reduce blood flow through kidney areas that are risk for hypoxic damage and tubular fluid flow is similarly affected. Traditional biomarkers of renal injury, including serum creatinine and blood urea have lacked the sensitivity and / or specificity to adequately detect nephrotoxicity prior to significant loss of renal function. The absence of sensitive and specific biomarkers for the early detection of acute kidney injury (AKI) has impaired progress in the diagnosis and treatment of patients with AKI. Therefore, there is a need to identify a more specific AKI biomarker that is produced at the site of injury and that can be measured easily in blood or urine and should be reasonably stable in body fluid to substantially improve the diagnosis.

Kidney Injury molecule -1 (KIM-1) as a type I membrane glycoprotein, which contain a 6- cystein immunoglobulin-like domain in its extracellular portion, and a Thr/Ser-Pro rich doain characteristic of mucin – like O-glycosylated proteins[3]. KIM-1 presence in the urine is highly specific for kidney injury. No other organs have been shown to express KIM-1 to a degree that would influence kidney excretion. Kidney Injury molecule - 1 (KIM-1) expression is induced in a variety of renal diseases, whereas in healthy kidney tissue KIM-1 is virtually undetectable[3-4]. In the case of kidney damage, KIM-1 is expressed on the apical membrane followed by cleavage of the ectodomain (90 kDa) which is released in the urine in humans[5-6].
 KIM-1 is upregulated in the proximal tubule during dedifferentiation of the kidney epithelium, an early manifestation in response to damage[7]. There is no studies to date that have examined KIM-1 for detection of AKI associated with contrast administration. There is an urgent need for improved and non-invasive renal biomarkers to permit early detection of AKI associated with contrast induced nephropathy. Kidney injury molecule (KIM-1) a transmembrane tubular protein, is undetectable in normal kidneys, but it is markedly induced in renal injury including acute kidney injury (AKI) and chronic kidney disease (CKD) [7-9]. Many studies indicate that KIM-1 is a sensitive and specific marker of kidney injury as well as a predictor of prognosis[10-11]. The above characteristics make KIM-1 an ideal marker for Acute Kidney injury (AKI). The objective of the present study was to examine the ability of KIM-1 in detecting contrast induced acute kidney injury. We assessed urinary KIM-1 values in relation to serum creatinine in these patients.

Table1: Basal clinical characteristics of patients undergoing angiography.

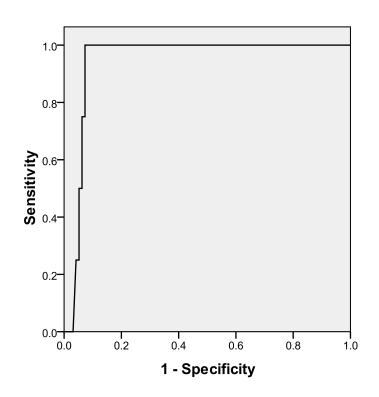| Parameter	Value
Age in years	48.6 ±11.0
Systolic BP, mmHg	136.5±29.0
Diastolic BP, mmHg	80.5±20.0
Heamoglobin, g/dl	14.5±2.0
HbA1c %	5.0±2.5
Serum creatinine, mg/dl	1.2±0.17
eGFR byMDRD equation, ml/min	81.2±22.0
Cholesterol, mg/dl	168±43
HDL, mg/dl	44±10
Fasting Blood Sugar, mg/dl	115±41

MATERIALS AND METHODS

The study was performed in one hundred consecutive patients undergoing angiographic procedure. The study was approved by the Ethics Committee of Micropath Medical Center, Gurgaon, Haryana. Written informed consent was obtained from each patient before enrolment. All consecutive adult patients undergoing coronary angiographic procedure from January, 2012 to April, 2013 were included. Clinical characteristics of all patients from whom urine was evaluated for KIM-1 are reported in Table No.1. Patients with diabetic mellitus comprised 38 of 21 male and 17 females. Patients with non-diabetic mellitus comprised 62 of 41 male and 21 females. Among diabetic patients, 14 were treated with insulin and the rest with oral hypoglycemic drugs.

 All subjects were discharged home from the angiography area after 8 hours of their procedure with advice to give specimen at scheduled time and encouraged to drink about 1.5 liters of water at least for the first 24 hours. The coronary angiography was performed by a consultant doctor in a standard manner using femoral artery. We excluded patients with pre-existing chronic kidney disease, serum creatinine greater than 1.5 mg/dl in males and 1.3 mg/dl in females. None of the subjects investigated had received nephrotoxic drugs at least 2 weeks before and during the study period. Before the procedure, all of the participating patients were given their urine and blood specimens for investigations such as cholesterol, High Density Lipoprotein, (HDL), Triglycerides, Hemoglobin, HbA1C and Fasting Blood Sugar (FBS). Blood pressure (BP) also studied on admission. Each patient was given low-osmolar contrast (iodizanol or iopromide) medium. Specific protocols and medications for contrast induced nephropathy prevention were not used in this study, but patients were persistently encouraged to drink plenty of fluids and oral fluid intake was maximally encouraged.

Blood samples were collected for serum creatinine and other screening evaluation before (at basal level). Thereafter urine samples were collected at 4 hours, 8 hours, 12 hours and 24 hours after the angiographic procedure. Urinary Samples were kept for 30 minutes at room temperature then supernatant was stored at -80 deg C. Serum creatinine was assessed before (at basal level), and 24h and 48 hours after the procedure using Jaffe method. Kidney Injury molecule (KIM-1) was evaluated using a commercially available enzyme-linked immunosorbent assay (USCN Life Science Inc, Wuhan 430056, P.R.China). KIM-1 test was performed according to manufactures instruction. For the choice of optimal cut-off, receiver operating characteristic (ROC) curve were constructed and the Youden index was calculated[12]. The Youden index is defined as follows: (sensitivity+specificity)-1. The best cut-off is the highest Youden index. The commercial statistical software package SPSS17.0 (SPSS, Inc, Chicago, IL, USA) was utilized. Results are evaluated with 95% confidence intervals. The significance level was< 0.05.

RESULTS

Clinical and biochemical characteristics of patients with normal serum creatinine values undergoing angiographic procedure are presented in Table 1. We found a significant rise in urinary KIM-1 at 24 h after the angiographic procedure. eGFR did not change significantly during 48 hours. When acute kidney injury was defined as an increase in serum creatinine by >25% of the baseline level 48 hours after contrast exposure, the prevalence of Acute Kidney Injury was 12%. The patients with AKI did not significantly differ with regard to age, blood pressure, serum creatinine, serum lipid levels before angiography when compared to patients without AKI. The serum creatinine levels 48 h after the angiography were significantly higher in the patients with AKI than in those without AKI (1.39±0.27vs1.12±0.17 mg/dl, p<0.001).

ROC Curve

Diagonal segments are produced by ties.

Fig.1: Receiver operative characteristics (ROC) showing curve against serum creatinine 48 hrs vs 24h urinary kim-1 and Contrast induced Acute Kidney Injury, defined as a serum creatinine increase by >25% of the baseline level 48 hours after angiographic procedure.. Using a cutoff value of 4.5 ng/ml, sensitivity, specificity and area under the receiver operating characteristic (ROC) curve for prediction of Acute Kidney Injury was very good urinary kim-1 at 24 hours (89%, 81% and 0.95 respectively).

The eGFR by MDRD formula 48 h after the angiography was significantly lower in the patients with AKI than in those without (63.45 ± 18.64 vs 82.95 ± 24.35 ml/min, p<0.05). The AKI was diagnosed in 12 patients at 24 hours following angiographic procedure. No significant differences were noted between patients with and without AKI in respect of age, sex , DM and Non-DM. (Table No.2). Urinary KIM-1 values were higher at 24h after the angiographic procedure. There was a mild increase in serum creatinine at 24h and milder at 48 hours after the angiographic procedure, but there was no significant increase in eGFR during 48 hours of the procedure.

We used AKI definition as rise in serum creatinine by >25%   over baseline, 48 hours after angiographic procedure. Patients after angiographic procedure are typically discharged within 48 hours sometimes even earlier, therefore, we could miss patients with AKI developing 48 hours after angiography. 24 hours after angiography, compared with the non-CIN group, urinary KIM-1 (ng/ml) levels of AKI group increased significantly 5.32 (4.64, 5.74) vs 4.24 (3.91, 4.61), P<0.05, the urinary KIM-1(ng/ml) levels were significantly

increased 5.32 ((4.64, 5.74) vs 3.31(2.73, 4.28), P<0.05, from levels of 4 hours to 24 hours after contrast administration in the AKI group.

Table: 2 Time course changes in serum creatinine and urinary KIM-1, eGFR and blood pressure (BP) in patients undergoing angiography.

Name of the parameter	Before angiography	After 2 hrs	After 4 hrs	After 8 hrs	After 24 hrs	After 48 hrs
Urinary KIM-1, ng/ml	ND	ND	3.1(2.54-4.16)	4.1(2.66-4..87)	5.31(4.53-5.74)	ND
Serum Creatinine, mg/dl	1.2±0.17	ND	ND	ND	1.21±0.26	1.32±0.27
eGFR by MDRD equation, ml/min	81.11±25.30	ND	ND	ND	77.8±25.32	80.13±24.38
Cystolic BP, mmHg	135.45±30.5	127.5±30.5	ND	ND	136.45±25.65	135.75±25.25
Diastolic BP, mmHg	81.5±23.5	80.5±21.5	ND	ND	81.5±16.4	81.65±13.55

ND: Not determined. Data given are mean values ± SD or median values (minimum-maximum).

Using the Youden index, the best cutoff value for urinary KIM-1 at 24 hours to predict acute Kidney Injury was: 4.5 ng/ml, with diagnostic sensitivity 89% and specificity 81%.

DISCUSSION

The traditional laboratory approach for detection of renal disease does not allow for early detection of acute renal injury. Damage to renal tubules can be insufficient to result in a change in a parameter of kidney function such as blood urea and serum creatinine. In addition, in cases of more extensive tubular injury, there is a lag in time between the injury and an increase in serum creatinine. RIFLE and AKIN Criteria: In 2002, the Acute Dialysis Quality Initiatives (ADQI) group proposed a standard definition and classification system for the syndrome of acute renal failure through a broad consus of experts across disciplines and international boundaries. The classification systems coins the acronym RIFLE and has three levels: risk, injury and failure; and two outcomes: persistent acute renal failure (termed loss) and End stage Kidney disease. A unique feature of the RIFLE classification is that it provides retrospectively for three grades of severity of renal dysfunction on the basis of a maximum change in serum creatinine, reflecting changes in GFR or duration and severity of decline in urine output from the baseline. Based on the findings that small alterations of serum creatinine result in adverse outcomes, the Acute Kidney Injury International collaborative Network (AKIN) recently changed the definition of Risk group to include patients with an increase in serum creatinine of 0.3 mg/dl[13]. The proposed diagnostic and staging criteria for AKI are designed to facilitate acquisition of knowledge and to validate the emerging concepts. Serum creatinine is the most widely used parameter for everyday assessment of glomerular filtration rate (GFR), but it has poor sensitivity and specificity in ARF because serum creatinine lags behind both renal injury and renal recovery[13]. Therefore, sensitive biomarkers of renal tubular injury are needed to detect early kidney injury.

About a decade ago, KIM-1 was discovered in the search for molecule involved in the pathogenesis of acute kidney injury. Ichimura et al. were the first to describe KIM-1 as a type I membrane glycoprotein, which contain a 6- cystein immunoglobulin-like domain in its extracellular portion, and a Thr/Ser-Pro rich domain characteristic of mucin –like O-glycosylated proteins[3]. KIM-1 presence in the urine is highly specific for kidney

injury. No other organs have been shown to express KIM-1 to a degree that would influence kidney excretion. In the study of nephrotoxicity, urinary KIM-1 levels increased severely earlier than the increase of blood urea nitrogen and plasma creatinine[7]. KIM-1 is also a tissue and urinary biomarker for nephrotoxicant-induced kidney injury. Tissue and urinary expressions were measured with different nephrotoxic doses of cisplatin, folic acids, cadmium, gentamycin, mercury and chromium[14-16.] In fact the Food and Drug Administration (FDA) and the European Medicines Evaluation Agency (EMEA) have included KIM-1 in the small list of kidney injury biomarkers that they will now consider in the evaluation of kidney damage as part of their respective drug review processes of new drugs. FDA News. FDA, European medicines agency to consider additional test results when assessing new drug safety collaborative effort by FDA and EMEA expected to yield additional safety data[17]. Therefore new promising markers were investigated to find the ways to diagnose Acute Kidney Injury at the earliest possible time. Serum creatinine levels began to rise within 24 hours in 80% of the patients, reaching maximum at 48-72 hours after contrast administration, returning to baseline after 2 weeks[13].

In our present study, the prevalence of AKI due to contrast administration was 12 %. The reported incidence of AKI due to contrast induced nephropathy varies widely, ranging from 0 to >50%[18]. This variability results from whether presence or absence of risk factors (primarily renal sufficiency), the definition of CIN, amount and type of contrast agent administered, the exact radiologic procedure and whether other causes of Acute Kidney Injury (AKI) unrelated to contrast media were excluded. There have been over 16 definitions used for the diagnosis of acute renal failure in previously published studies, with most of them based on serum creatinine values. Recently the Acute Kidney injury Network has supported the use of the term 'acute kidney injury' to reflect the broad spectrum of acute kidney disease, including conditions that do not progress to failure[19].

In a study conducted by WK Han, et al revealed that the Urinary KIM-1 increased at 6-12 h after cardio-pulmonary bypass surgery (CPB) and remained significantly elevated upto 48 hours after CPB. In their study urinary KIM-1 had an AUC-ROC of 0.57 at 2h, 0.83 at 12 h, and 0.78 at 24 h[20]. Nejat M et al found in a study that the Kidney injury molecule-1 (KIM-1) is elevated in pre-renal azotemia to a lesser extent than in more severe AKI (lasting more than 48 hours) [21]. Therefore, the heterogeneity of AKI suggests that more than one marker may be necessary to obtain sufficient sensitivity and specificity for AKI screening. Analysis of multiple biomarkers such as NGAL, Cystatin C with KIM-1 may optimize early detection of AKI associated with contrast administration at the earliest.

CONCLUSION:

Kidney injury molecule-1 is an epithelial cell adhesion molecule that is induced in damaged tubular epithelial cells undergoing dedifferentiation and proliferation and the role of KIM-1 as a biomarker has a roubust future. The present study revealed that the urine KIM-1 at 24 hours after angiographic procedure can detect acute Kidney Injury associated with contrast administration earlier than serum creatinine. Limitation of this study is that we could not include L-FABP which is a new marker for acute Kidney Injury and We could have missed patients who developed acute Kidney Injury after 48 hours of the procedure. In summary, this is the first study to test the efficiency of new bio-markers in this setup revealing advantages of urinary KIM-1. The population studied is not representative of the global group of patients with AKI associated with Contrast administration.

Our findings may have important implications for the clinical management of patients undergoing angiographic procedure. Further studies in patients undergoing radio-contrast administration are required to assess the usefulness of KIM-1 as a biomarker for early diagnosis.

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