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Serum neutrophil gelatinase associated lipocalin (NGAL) and cystatin C as early predictors of contrast-induced acute kidney injury in patients undergoing percutaneous coronary intervention

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ABSTRACT

Background: Contrast-induced acute kidney injury (AKI) is diagnosed by estimating serum creatinine at 48–72 h after diagnostic or interventional coronary angiography. It is too late for an early intervention. Neutrophil gelatinase associated lipocalin (NGAL) and cystatin C are novel markers of AKI. We determined the optimum cut-off level of NGAL and cystatin C in early diagnosis and prediction of AKI in patients undergoing coronary angiography followed by angioplasty.
Methods: In a nested case control study, serum NGAL, cystatin C by ELISA and serum creatinine by Jaffe's kinetic method were estimated at 0, 4, 24 and 48 h of coronary angiography followed by angioplasty in 30 cases who developed contrast-induced AKI and 30 subjects who did not develop AKI. eGFR was estimated for both cases and controls by the MDRD equation. ROC was used to determine the optimum cut-off.
Results: Serum NGAL increased sharply at 4 h after the procedure and then gradually declined to near normal level at 48 h in AKI cases. The rise in cystatin C peaked at 24 h and then declined but remained high till 48 h. In controls, they remained static. The optimum cut-off of serum NGAL and cystatin C was 155.2 ng/ml and 0.517 mg/l respectively at 4 h and 89.5 ng/ml and 0.99 mg/l respectively at 24 h of angiography. Odds ratio for hypertensives to develop AKI was 3.57 (CI: 1.2–11.1, $p = 0.03$).
Conclusion: Serum NGAL and cystatin C may act as early markers of contrast-induced AKI in patients undergoing percutaneous coronary intervention. Patients with hypertension are susceptible to develop contrast-induced AKI.

1. Introduction

Contrast-induced nephropathy (CIN) is the third most common cause of hospital-acquired acute kidney injury (AKI) [1–3]. An increasing number of individuals are now getting exposed to iodinated contrast media [2,4]. Incidence of hospital acquired AKI is reported to be nearly 11% [1,2] and half of the cases are due to cardiac catheterization and angiography and one-third due to contrast-enhanced computed tomography. In this condition, an acute decrease in renal function occurs after intravascular administration of contrast media in the absence of other causes [5]. It is defined as an increase in concentration of serum creatinine at least by 0.5 mg/dl (or 44 mmol/l) or a ≥25% relative increase of serum creatinine from the baseline, 48–72 h after a diagnostic or interventional procedure [6,7]. Although serum creatinine is not an ideal marker of acute reduction in GFR, serial measurement of serum/plasma creatinine is the best way to assess any deterioration of GFR. It is widely used and most reliable marker of renal failure [8,9]. Acute kidney injury is largely asymptomatic and current diagnostic standards rely on changes in serum creatinine in serial measurements as a reflection of acute reduction in glomerular filtration rate (GFR) [10]. But this causes a delay in diagnosis of contrast-induced AKI, which affects the treatment and corrective interventions. So there is an immense need for a biomarker that can overcome this limitation.

Neutrophil gelatinase associated lipocalin (NGAL) is a small (25 kD) molecule that belongs to lipocalin-2 super family. It is normally expressed at very low levels in several human tissues including the kidney [11]. Its expression is markedly induced in injured epithelia. It is one of the earliest and most robustly induced genes in the kidney after ischemic or nephrotoxic injury in animal models [7]. It is easily detected in the blood and urine soon after acute kidney injury [12,13] and is being evaluated as an early predictor of AKI in different clinical conditions [14–17].

Cystatin C is a 13 kDa non-glycosylated protein belonging to the cysteine protease inhibitors [18]. It is produced by all nucleated cells at a constant rate and removed from the blood by glomerular filtration. Cystatin C is considered as a reliable marker for GFR and renal function and is an early predictor of AKI [19–21]. Although useful, no standard

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cut-off levels have yet been determined for these biomarkers in predicting AKI.

2. Methods

It was a nested case control study where patients undergoing percutaneous coronary intervention (PCI) were recruited till 30 cases of contrast-induced AKI were detected. A total of 250 patients were recruited to obtain 30 such cases. Patients with any pre-existing chronic nephropathy (serum creatinine > 1.2 mg/dl) including diabetic nephropathy, any systemic infection and urinary tract infection were excluded. The cases of contrast-induced AKI were detected by a rise in serum creatinine level of at least 0.5 mg/dl from the baseline value at 48 h after PCI and 30 controls were randomly chosen from the recruited patients who did not develop contrast-induced AKI. The distribution of sex ratio (whole population: males—82.4%, females—17.6%, controls: males—83.3%, females—16%; p value = 0.8), hypertension (whole population: 31%, controls: 30%; p value = 0.9), diabetes (whole population: 14%, controls 13%; p value = 0.8) and serum creatinine level (whole population: mean—0.78 ± 0.18 mg/dl, controls: mean—0.82 ± 0.18 mg/dl; p value =0.3) in controls (n = 30) were not different from those of the total population (n = 220).

Informed written consent was taken from the subjects involved in the study. The study was approved by ethical committee of institution (Ref. No. F11/IEC/MAMC/10/14247). For angiography followed by angioplasty, a standard dose (3–5 ml/kg) of iodinated contrast medium (Omnipaque, GE Healthcare Pvt. Ltd.) was used.

Venous blood sample of 3 ml was collected from each patient for estimation of serum NGAL, cystatin C and creatinine at 0 h (baseline), 4, 24 and 48 h of angioplasty procedure. Serum was separated by centrifuging the blood for 10 min at room temperature, serum creatinine was estimated by Jaffe's method adapted to Beckman Coulter DXC 800 random access clinical chemistry analyzer (Beckman Coulter) and the rest of the serum was stored at −80 °C until analyzed. After selection of cases and controls, their serum level of NGAL and cystatin C was assayed by the sandwich ELISA kit method (Biovendor) adapted to ELISA reader instrument (Bio-Rad). Two milliliters blood in NaF containing vial was used for estimation of baseline plasma random glucose levels and 2 ml blood collected in EDTA vial was used for HbA_{1C} estimation.

Serum creatinine, urea, total cholesterol, triglycerides, HDL-C, LDL-C, CK-MB, albumin, and random glucose estimation were done using commercial kit on the Beckman Coulter DXC 800. Hb estimation was done by the cyanmethemoglobin method. HbA_{1C} estimation was done by the HPLC method using Bio-Rad. eGFR was calculated by the Modification of Diet in Renal Disease (MDRD) study equation.

2.1. Statistical analysis

The data was expressed as mean and SD. Categorical data was expressed as percentage. Repeated measures ANOVA and unpaired *t* test were used for comparison of data as applicable. ROC was drawn to detect the optimum cut-off of parameters and their sensitivity and specificity in predicting contrast-induced AKI. The results were considered significant when the p value was <0.05. SPSS PC ver 17 was used for all statistical analyses.

Table 1
Demographic profile of the contrast-induced acute kidney injury (AKI) cases and controls.

	Cases (AKI) (n = 30)	Controls (non-AKI) (n = 30)	p value[a]
Age (mean ± SD)	57.63 ± 7.36	54.17 ± 9.35	0.11
Sex (m:f)	21/9	23/7	0.55

[a] p value by independent samples *t* test (for age) and Pearson χ^2 test (for sex).

Table 2
Clinical profile of the contrast-induced acute kidney injury (AKI) cases (n = 30) and controls (n = 30).

	Cases (AKI)	Controls (non-AKI)	p value
No. of hypertensive subjects	18	9	0.02[a]
No. of smokers	12	12	NS[a]
No. of alcoholics	7	6	NS[a]
Diabetics	3	4	NS[b]
Findings on angioplasty			NS
No. of single vessel disease	4	8	
No. of double vessel disease	18	19	
No. of triple vessel disease	8	3	
Volume of contrast (ml), (mean ± SD)	182.67 ± 48.91	155.0 ± 42.24	0.02[c]

[a] p value calculated by using the Pearson χ^2 test.
[b] p value calculated by Fisher's exact test.
[c] p value calculated by independent samples *t* test.

3. Results

A total of 250 subjects planned for elective PCI were screened for the presence of AKI after the infusion of contrast medium, of which 30 were found to develop AKI according to the definition (0.5 mg/dl increase in the serum creatinine level from the baseline value 48 h after the infusion of contrast medium). The rest of 220 subjects did not show a significant rise in the levels of serum creatinine as defined above. Of these 220 patients, 30 subjects were selected randomly as controls. Demographic profile of the AKI patients group showed no significant difference in the mean age and sex ratio with those of controls (Table 1).

Clinical profile of the study groups is shown in Table 2. Patients suffering from hypertension were significantly more in the AKI group (n = 18) than in control group (n = 9). Odds ratio was 3.57 (CI: 1.2–11.1, P = 0.03). There were equal number of smokers and comparable number of alcoholics and diabetics in both groups. The number of vessels affected for which angioplasty procedures performed was not significantly different (Table 2).

The results of preoperative routine baseline investigations are shown in Table 3. All parameters except baseline serum cystatin C level were comparable in both groups. Hb%, serum urea, creatinine, eGFR, cholesterol, HDL-C, LDL-C, albumin, plasma random glucose, HbA_{1C}, and serum CK-MB were not different in both groups. Variations in serum creatinine in both groups after PCI are shown in Table 4. The rise in serum creatinine at 48 h in AKI group was higher than the baseline (0 h) value. In controls, the variation in serum creatinine level is not significant.

Table 3
Mean and SD of baseline laboratory profile before contrast infusion of the contrast-induced acute kidney injury (AKI) cases and controls.

	Cases (AKI) (n = 30)	Controls (non-AKI) (n = 30)	p value[a]
Hb (mg/dl)	13.47 ± 1.47	13.29 ± 1.65	NS
Sr. urea (mg/dl)	34.37 ± 8.25	31.43 ± 6.86	NS
Sr. creatinine (mg/dl)	0.86 ± 0.24	0.82 ± 0.19	NS
eGFR (ml/min/1.73 m^2)	98.63 ± 32.46	111.2 ± 29.8	NS
Sr. cholesterol (mg/dl)	121.10 ± 18.84	121.33 ± 26.47	NS
Sr. TAG (mg/dl)	89.9 ± 31.27	85.40 ± 16.55	NS
Sr. HDL-C (mg/dl)	28.58 ± 9.2	27.27 ± 4.75	NS
Sr. LDL-C (mg/dl)	74.73 ± 14.92	74.79 ± 23.17	NS
Sr. albumin (mg/dl)	3.37 ± 0.56	3.46 ± 0.47	NS
Plasma random glucose (mg/dl)	113.87 ± 13.53	107.83 ± 14.46	NS
HbA_{1C} (%)	4.99 ± 0.65	4.89 ± 0.63	NS
Sr. CK-MB (mg/dl)	26.30 ± 18.16	25.25 ± 19.39	NS
Sr. NGAL (ng/ml)	70.41 ± 28.67	72.72 ± 28.72	NS
Sr. cystatin C (ng/ml)	619.37 ± 258.86	397.12 ± 256.11	0.001

[a] p value by independent samples *t* test.

Table 4
Mean and SD of serum creatinine (mg/dl), NGAL (ng/ml) and cystatin C (mg/l) levels at 0, 4, 24 and 48 h of percutaneous coronary intervention in AKI group (n = 30) and non-AKI controls (n = 30).

		0 h	4 h	24 h	48 h
Serum creatinine (mg/dl)	Controls	0.82 ± 0.19	0.69 ± 0.16	0.73 ± 0.17	1.09 ± 0.22
	AKI cases	0.86 ± 0.24	0.62 ± 0.22	0.91 ± 0.25	1.57 ± 0.34*
Serum cystatin C (mg/l)	Controls	0.397 ± 0.25	0.413 ± 0.25	0.446 ± 0.25	0.402 ± −0.25
	AKI cases	0.619 ± 0.25Ψ	0.653 ± 0.27	3.665 ± 1.21*	2.045 ± 0.97*
Serum NGAL (ng/ml)	Controls	72.72 ± 28.72	74.90 ± 24.33	75.97 ± 28.58	72.53 ± 28.39
	AKI cases	70.41 ± 28.67	259.28 ± 54.56*	103.23 ± 25.63*	74.90 ± 24.33

* p = 0.000 in comparison to respective 0 h value by repeated measure ANOVA.
Ψ p = 0.001 in comparison to control by unpaired *t* test.

Serum cystatin C and NGAL levels at 0, 4, 24 and 48 h are depicted in Table 4 and Figs. 1 and 2. The rise in serum NGAL in AKI group was the maximum at 4 h which was significantly higher than 0 h level. The level declined at 24 h but still remained significantly higher than 0 h level. The level reached near baseline at 48 h. Serum cystatin C level in AKI group increased maximally at 24 h. The value declined at 48 h but still remained higher than 0 h level. The variation of serum NGAL and cystatin C levels was not significant in controls.

The result of ROC analysis of serum NGAL at 4 h, 24 h and 48 h are summarized in Table 5. At a cut-off level of 155.2 ng/ml, serum NGAL at 4 h has sensitivity and specificity of 100% and 96.7% respectively in differentiating AKI from controls. The AUC of ROC was 1.00 (p = 0.000). At 24 h, serum NGAL has an AUC of 0.694 (p = 0.002) and an optimum cut-off of more than 89.5 ng/ml with sensitivity and specificity of 63.3% and 53% respectively. At 48 h, the AUC of ROC was not significant.

The result of ROC analysis of serum cystatin C levels at 0, 4 and 24 h are shown in Table 5. For ROC of serum cystatin C, the AUC at 0, 4, 24 and 48 h was 0.701 (p = 0.002), 0.724 (p = 0.001), 1.00 (p = 0.000) and 0.996 (p = 0.000) respectively and the optimum cut-off levels were 0.504 mg/l (sensitivity = 66% and specificity = 63%), 0.517 mg/l (sensitivity = 66.7% and specificity = 66.6%), 0.994 mg/l (sensitivity = 100% and specificity = 96.7%), and 0.961 mg/l (sensitivity = 93.3% and specificity = 96.7%) respectively for differentiating AKI and non-AKI patients.

4. Discussion

The occurrence of contrast-induced AKI following percutaneous coronary intervention (PCI) was 12% which is very similar to that in other studies conducted previously [1,2,5,22,23]. The age and sex distribution was similar in AKI and non-AKI group (Table 1). The number of diabetics, smokers and alcoholics was equally distributed in both the groups and the number of vessels affected in the heart was also evenly distributed in both the groups (Table 2). Their random plasma glucose levels and other laboratory parameters except cystatin C were not different (Table 3). So these were not the confounders in the present study. The normal basal serum urea, creatinine, eGFR and NGAL indicate that none of the subjects had any significant impairment of renal function before PCI. The significant rise in serum creatinine in AKI group (Table 4) indicates that they developed contrast-induced nephropathy, whereas the rise was not significant in controls indicating that their renal damage was not significant enough to qualify them as AKI patients according to definition. The small rise in serum creatinine levels in the control group probably indicates that some amount of renal injury, however small, occurs in all subjects exposed to contrast media. This injury is probably very mild and transient with no subsequent aftereffects on the renal function. The small decrease in serum creatinine at 4 h may be because of dilution effect of intravenous fluid given during the procedure and immediate post-operative period.

Odds ratio for hypertensive patients to develop AKI was 3.57 (CI: 1.2–11.1, P = 0.03). It indicates that the hypertensive patients are predisposed to contrast-induced AKI. Hypertension is a known risk factor for some degree of renal dysfunction despite normal baseline serum creatinine level. A similar observation was made in a study by Bachorzewska-Gajewska et al. [16] and Shaker et al. [7]. Hypertension, per se, increases serum cystatin C levels [21,24,25]. Although the serum level of cystatin C is predominantly determined by GFR, age, sex, diabetes and pro-inflammatory state are known confounders that influence serum cystatin C level [26]. Hypertension is a pro-inflammatory state associated with the rise in serum markers of inflammation like CRP and TNF-α [27,28]. Although within normal range, a relatively high basal level of serum cystatin C in AKI group might be because of more number of hypertensive patients in this group. The result of ROC drawn from the basal serum cystatin C levels indicates that this parameter has potential in predicting AKI in patients undergoing PCI where iodinated contrast is used. The optimum cut-off of baseline serum cystatin C was 0.504 mg/l which is within the reference interval. Its sensitivity and specificity were also low. Hence its clinical utility is doubtful and needs to be further evaluated with a bigger sample size.

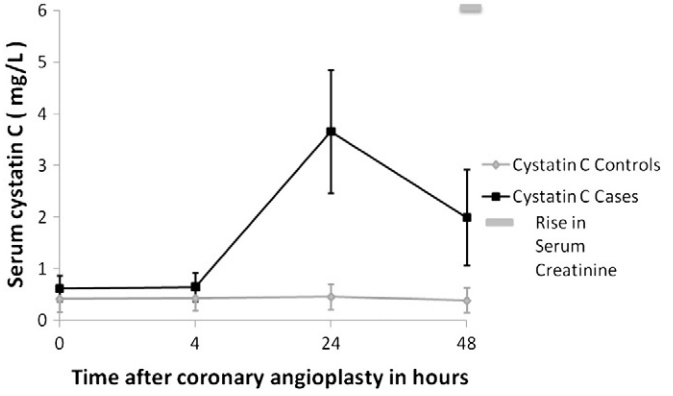

Fig. 1. Analysis of serum cystatin C by ELISA. Graph shows the mean serum cystatin C concentrations at various time points after coronary angioplasty in cases and controls.

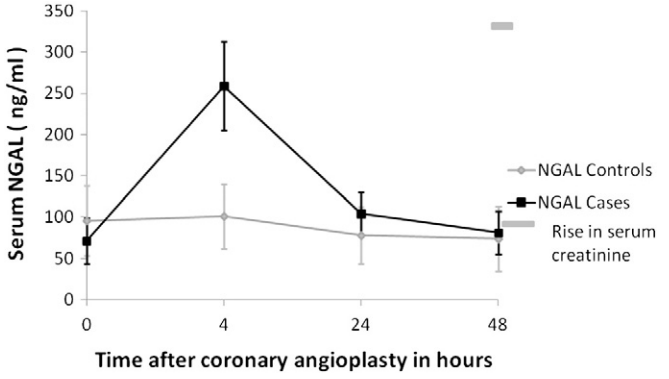

Fig. 2. Analysis of serum NGAL by ELISA. Graph shows the mean serum NGAL concentrations at various time points after coronary angioplasty in case and control groups.

Table 5
Area under curve (AUC), its p value and optimum cut-off, and its sensitivity and specificity of ROC analysis of NGAL and cystatin C for the of contrast-induced acute kidney injury in patient undergoing coronary angiography followed by angioplasty.

	AUC	p value	Cut-off	Sensitivity	Specificity
NGAL 4 h	1.00	0.000	>155.2 ng/ml	100%	96.7%
NGAL 24 h	0.694	0.002	>89.5 ng/ml	63.3%	53%
NGAL 48 h	0.513	NS	–	–	–
Cystatin C 0 h	0.701	0.002	>0.504 mg/l	66%	63%
Cystatin C 4 h	0.724	0.001	>0.517 mg/l	66.7%	66.6%
Cystatin C 24 h	1.00	0.000	>0.994 mg/l	100%	96.7%
Cystatin C 48 h	0.996	0.000	>0.961 mg/l	93.3%	96.7%

In previous studies, increase in the level of serum creatinine from the baseline value was used as a "gold standard" to diagnose contrast-induced AKI [29,30]. Contrast infusion causes rapid changes in the renal hemodynamic which later on causes a decrease in GFR that may lead to AKI [31]. Studies have proven that during the early damage stage, only subtle and largely reversible changes (like alteration in cell polarity and micro-vascular perturbations) are detected. Therapeutic interventions done at this stage have been successful in preventing and treating AKI in many experimental studies [32]. However, once AKI sets in, more severe and irreversible changes such as intra-tubular obstruction, desquamation and cell death become apparent. Most therapeutic interventions initiated in the established phase of AKI have been unsuccessful [32]. Although serial serum creatinine estimation eliminates most of the limitations of serum creatinine [8], it detects AKI after 48–72 h of contrast infusion. By this time, significant irreversible changes occur in the kidney. Hence, there is a need of suitable biomarkers for an early diagnosis of the AKI induced by contrast medium in PCI. Biomarkers like NGAL and cystatin C have been studied to evaluate their role as early predictors of AKI, but timing of their measurement, sensitivity, specificity and cut-off values varied from study to study [14–16,33,34]. Also, there is a paucity of information on this subject in Indian population where the study was conducted. From the ROC (Table 5), it is revealed that serum NGAL can detect contrast-induced AKI within 4 h of PCI. This is the earliest that any maker can detect AKI with such high level of sensitivity and specificity. Nearly similar findings were observed in previous studies [14,15,34]. This can detect AKI from the sample collected till 24 h after PCI. But the disadvantage of NGAL is that it returns to near normal level by 48 h and hence has a narrow diagnostic window (Fig. 2). Besides the fall in GFR, induction of NGAL by insult to renal tissue might also contribute to the rise in serum NGAL and this induction of NGAL probably signifies a step to preserve normal function of the affected organ as NGAL is known to have a protective effect against ischemia-induced renal damage [35]. This protective effect of NGAL is dependent on the chelation of toxic iron from extracellular environments and the regulated delivery of siderophores (the small-iron binding molecules and the major ligands for NGAL) and iron to intracellular sites [36–38]. This makes NGAL a promising candidate for early detection of any kind of insult to renal parenchyma.

Cystatin C is taken up by the PCT and completely catabolized there [39]. It does not undergo tubular secretion and appears in the urine through filtration [40,41]. The involvement of PCT in the reuptake process suggests that the measurement of urinary cystatin C may provide information on tubular function also [42,43]. So, in contrast-induced kidney injury, damage either to the glomerulus or tubules may lead to the increase in the levels of serum cystatin C as found in AKI cases in the present study (Fig. 1 and Table 4). Pro-inflammatory state, diabetes, age, gender and race were found to be associated with high level of cystatin C [26]. The rise in cystatin C was maximum at 24 h in the present study. It has a wide diagnostic window but the cut-off value has maximum sensitivity and specificity at 24 h. So it can best detect AKI at 24 h of PCI which is earlier than when serum creatinine can detect it. Similar findings were observed by many researchers [7,33,34,44]. So objectively as a marker, NGAL appears to be superior to cystatin C in early detection of contrast-induced AKI. One limitation of this study is that cystatin C was measured by the ELISA method which is less precise than the nephelometric or turbidimetric method.

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