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Evaluation of a Diagnostic Test of Serum Neutrophil Gelatinase-Associated Lipocalin (NGAL) and Urine KIM-1 in Contrast-Induced Nephropathy (CIN)

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Statistical Analysis C
Data Interpretation D
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Background: The aim of this study was to assess changes in serum neutrophil gelatinase-associated lipocalin (NGAL) and urine KIM-1 after percutaneous coronary intervention (PCI).

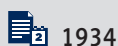
Material/Methods: A total of 240 patients receiving coronary stent implantation were selected. All patients were divided into 2 groups: a CIN group (n=25) and a non-CIN group (n=215). The serum creatinine (SCr), NGAL, and urine KIM-1 levels of the patients in both groups were measured before and after surgery, and the sensitivity of serum NGAL and urine KIM-1 in diagnosing CIN in the early stage was assessed by the area under receiver operating characteristic (ROC) curve (ROC-AUC).

Results: In the CIN group, the serum NGAL and urine KIM-1 levels started to rise at 6 h after surgery. The serum NGAL and urine KIM-1 levels in CIN group were significantly higher than those in the non-CIN group at 6, 12, 24, and 48 h after surgery. However, the SCr levels in the CIN group were not higher than those in the non-CIN group at 6 h after surgery. At 6, 12, and 24 h after PCI, the AUCs for serum NGAL and urine KIM-1 were increased compared with that for SCr, while the AUCs for serum NGAL and urine KIM-1 were decreased at 48 h after PCI compared with that for SCr.

Conclusions: Serum NGAL and urine KIM-1 levels in the patients after coronary stent implantation can reflect the changes in renal functions early, thus providing a certain basis for the early diagnosis of CIN.

MeSH Keywords: **Acute Kidney Injury • Creatinine • Percutaneous Coronary Intervention**

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Background

With the current rapid development of medical science, interventional techniques have been extensively applied to diagnose and treat diseases, and this has led to increased numbers of contrast-induced nephropathy (CIN) cases [1–3]. Studies have shown that acute kidney injury (AKI) triggered by CIN accounts for 11% of the total cases, becoming the third most important cause of iatrogenic AKI [4]. Currently, clinically significant damage is defined as impairment of renal function occurring within 48 h after administration of contrast media, manifested by an absolute increase in the serum creatinine (SCr) level of at least 44 $\mu\text{mol/L}$ or by a relative increase of at least 25% over the baseline value in the absence of another cause. However, SCr has low sensitivity and specificity in the early diagnosis of CIN [5]. Therefore, diagnosing CIN in the early stage becomes particularly significant. Studies have proven that neutrophil gelatinase-associated lipocalin (NGAL) and KIM-1 are superior to traditional SCr in early diagnosis of AKI. In the present study we assessed serum NGAL and urine KIM-1 levels in patients after percutaneous coronary intervention (PCI) to explore their utility in the early diagnosis of CIN.

Material and Methods

Subjects

A total of 240 patients undergoing PCI at Qinghai Provincial People's Hospital from January 2017 to January 2018 were selected, including 128 males and 112 females aged 60.92 ± 6.38 years old. All the patients met the diagnostic criteria of coronary heart disease and had indications for coronary stent implantation. Exclusion criteria were: 1) patients with AKI caused by pre-renal, renal, or post-renal obstruction, 2) patients using nephrotoxic drugs or contrast media within 2 weeks before surgery, 3) patients with severe heart failure or other organ failures, 4) patients with acute myocardial infarction, and 5) patients with acute infection. In this study, all diabetic patients took oral hypoglycemic agents (e.g., biguanides, sulfonylureas, glinides, α -glycosidase inhibitors, dipeptidyl peptidase IV inhibitors), and some of them also used insulin analogues in the hypoglycemic treatment. The overall glycosylated hemoglobin level of included DM patients was $(6.8 \pm 0.9)\%$. CIN refers to the fact that, on the premise of excluding other causes, the SCr level increases by 0.5 mg/dL (44 $\mu\text{mol/L}$), or by 25% compared with the baseline value, within 72 h after intravascular injection of iodine contrast agent. The name, sex, age, underlying diseases, dose of iodine contrast agent, and relevant laboratory examination results of the patients were collected. Signed written informed consent was obtained from all participants before the study. This study was approved by the Ethics Committee of Qinghai Provincial People's Hospital (CN-QH-2016-075293).

Methods

Specimen collection: We collected 5 mL venous blood and 10 mL urine specimens from all subjects before angiography and at 6 h, 12 h, 24 h, and 48 h after angiography. Specimen were centrifuged at 4000 rpm for 10 min, then supernatant was placed into sterile EP tubes, which were labeled and stored at -80°C for centralized detection and avoidance of repeated freezing and thawing.

Specimen detection: We used a HITACHI7080 full-automatic biochemistry analyzer (Hitachi, Tokyo, Japan) for biochemical assessment. The picric acid rate method was used for SCr detection. The NGAL and KIM-1 levels were determined by ELISA according to the experimental procedures in the reagent instructions, and the corresponding level in each sample was calculated on the basis of the absorbance detected.

Area under receiver operating characteristic (ROC) curve (ROC-AUC): In order to determine the sensitivity and specificity of serum NGAL, SCr, and urine KIM-1 in diagnosing CIN at different time points after PCI, the AUCs for serum NGAL, SCr, and urine KIM-1 at different time points after PCI were calculated separately, with the test results of the CIN patients as the demarcation points.

Statistical analysis

All statistical analyses were performed using SPSS 19.0 software (IBM, Armonk, NY, USA). Normally-distributed quantitative data are expressed as mean \pm standard deviation ($\bar{x} \pm s$), and the *t* test was used to compare differences between groups. Rates were compared using the chi-square test. Non-normally distributed data were compared by Mann-Whitney rank sum test. Statistical significance was set at $P < 0.05$.

Results

General data

Among the 240 patients, 25 had CIN, including 15 males and 10 females, aged (63.27 ± 5.79) years old, with an incidence rate of 10.42%. There were 8 cases of hypertension, 12 cases of diabetes mellitus, and 4 cases of hyperlipidemia. Data on sex, age, underlying diseases, doses of iodine contrast agent, and length of hospital stay were collected. In the CIN group, diabetes mellitus was a more common underlying disease, and the hospital stay was longer. The differences in hypertension, hyperlipidemia, dose of iodine contrast agent, and SCr, NGAL, and KIM-1 levels at admission between the 2 groups were not statistically significant ($P > 0.05$) (Table 1).

Table 1. Baseline characteristics of included subjects.

	CIN group	Non-CIN group	t/ χ^2 /Z	P
n	25	215		
Age(y)	63.19±5.87	60.25±6.61	2.138	0.32
Male, n(%)	15 (60)	108 (50.23)	0.874	0.41
Diabetes mellitus, n (%)	12 (48)	49 (22.79)	3.626	0.03
Hypertension, n (%)	8 (32)	80 (37.21)	0.901	0.69
Hyperlipidemia, n (%)	4 (16)	44 (20.47)	0.347	0.57
Dose of iodine contrast agent (mL)	207.58±28.04	200.26±26.73	1.285	0.23
Length of hospital stay (d)	16.34±3.07	9.84±2.51	14.783	<0.01
Scr at admission (umol/L)	67.69±11.23	65.65±8.02	0.562	0.72
NGAL at admission (ng/mL)	88.75±14.78	86.19±13.86	1.719	0.50
KIM-1 at admission (mg/L)	28.28±4.47	27.35±3.96	3.624	0.83

$P < 0.05$ suggested statistically significant.

Changes in SCr, NGAL, and KIM-1 at different time points after PCI

In the CIN group, serum NGAL and urine KIM-1 levels started to rise at 6 h after surgery, reached the peak at 12–24 h after surgery in the CIN group, and then began to decline at 48 h after surgery. Compared with those in the non-CIN group, the serum NGAL and urine KIM-1 levels were elevated at 6, 12, 24, and 48 h after surgery in the CIN group, and the differences were statistically significant ($P < 0.05$). However, at 6 h after surgery, SCr levels in the CIN group were not higher than those in the non-CIN group, with no statistically significant differences ($P > 0.05$) (Table 2).

ROC-AUC for SCr, NGAL, and KIM-1 at different time points after PCI

AUCs for NGAL, KIM-1 and SCr were 0.81, 0.74, and 0.58 at 6 h after surgery, 0.89, 0.84 and 0.79 at 12 h after surgery, 0.89, 0.87 and 0.86 at 24 h after surgery, and 0.79, 0.72, 0.87 at 48 h after surgery, respectively. AUCs for serum NGAL and urine KIM-1 were larger than that for SCr at 6, 12, and 24 h after PCI, and the AUCs for serum NGAL and urine KIM-1 were smaller than that for SCr at 48 h after PCI (Table 3). According to the analysis on the ROC curves at different time points, NGAL had the highest specificity and sensitivity at 12 and 24 h after surgery.

Discussion

The clinical diagnosis of CIN mainly depends on the changes in SCr level, but the difference in SCr sensitivity cannot diagnose

CIN in the early stage, so it is especially important to find biomarkers for diagnosis of early CIN [5]. NGAL, a member of the lipocalin family, is widely distributed in various tissues in the body, such as the bronchus, gastrointestinal tract, and renal tubule. It is capable of inducing the differentiation of renal progenitor cells toward renal tubular epithelial cells, so as to repair and regenerate the impaired renal tubular epithelial cells. Moreover, in case of renal tubular impairment, the elevated serum NGAL level can promote repair and regeneration of the renal tubule. It has been reported that the serum NGAL level is increased markedly in AKI patients, and decreases to normal level as renal function is recovered. These studies show that serum NGAL level is able to serve as an early diagnostic marker for AKI [6–8].

As CIN has become a common cause of hospital-acquired AKI, can NGAL be applied to diagnose CIN in the early stage? Studies have revealed that the NGAL level rises in blood and tissues of CIN rat models at 2 h after the occurrence of CIN, while the SCr starts to increase at 48 h [5,9]. For children with CIN, the serum NGAL level is increased at 2 h after the application of contrast media, and the SCr level is elevated at 12–24 h [10]. The NGAL level in patients with CIN is elevated at 8 h after surgery, while the SCr level is increased at 24 h after surgery [6]. The ROC curves show that the sensitivity and specificity of serum and urine NGAL are relatively high. According to multiple systematic reviews, the NGAL level in the serum or urine possesses fairly high specificity and sensitivity in the early diagnosis of CIN [4]. The NGAL level starts to rise at 6 h after interventional operations in the CIN group compared with that in the control group. Filiopoulos et al. [11] found that in CIN caused by CT angiography in the hospital, the plasma NGAL

Table 2. Changes of bio-marker levels at different time points after PCI.

	CIN group	Non-CIN group
Serum SCr (umol/L)		
0 h	65.84±7.31	68.25±10.52
6 h	71.18±9.23	69.83±11.95
12 h	85.52±11.09	73.26±10.86
24 h	105.87±44.42	72.89±10.73
48 h	116.35±43.04	77.98±11.97
Between groups	$F=112.894, P<0.05$	
Between time points	$F=36.380, P<0.05$	
Between groups*Between time points	$F=22.173, P<0.05$	
Serum NGAL(ng/mL)		
0 h	86.78±13.96	87.69±15.85
6 h	126.05±55.41	88.87±4.23
12 h	167.27±89.37	88.05±5.26
24 h	162.84±76.28	89.12±5.35
48 h	123.36±55.42	87.53±4.98
Between groups	$F=208.156, P<0.05$	
Between time points	$F=37.825, P<0.05$	
Between groups*Between time points	$F=24.392, P<0.05$	
Urine KIM-1 (ng/L)		
0 h	28.28±4.47	27.35±3.96
6 h	64.33±9.58	37.32±6.45
12 h	74.23±10.86	40.19±9.47
24 h	71.46±9.62	41.31±7.63
48 h	54.52±7.87	39.02±6.01
Between groups	$F=98.261, P<0.05$	
Between time points	$F=21.473, P<0.05$	
Between groups*Between time points	$F=23.348, P<0.05$	

$P<0.05$ suggested statistically significant.

is increased at 6 h after angiography. The above studies show that serum NGAL is more sensitive than SCr in diagnosing early CIN. It was also confirmed in this research that the serum NGAL and urine KIM-1 levels began to increase at 6 h after surgery in the CIN group compared with those in the non-CIN group. Serum NGAL and urine KIM-1 peaked at 12–24 h after surgery, and then began to decline at 48 h after surgery. In the CIN group, the rise in SCr was not significant at 6 h after surgery.

Previous studies have found that serum NGAL and urine KIM-1 diagnose early CIN 24 hours earlier than does SCr [5]. According to research in patients with CIN, the serum NGAL level is increased first at 6 h after the application of contrast media, while the urine KIM-1 level is elevated at 12 h after

the application of contrast media. As a result, serum NGAL and urine KIM-1 in the serum are increased within the first 24 h after the use of contrast media. However, some studies have found that the level of NGAL in serum and urine after PCI in elderly patients did not increase significantly, while KIM-1 was significantly increased [12].

KIM-1 is an epithelial cell adhesion molecule present in CD4 T lymphocytes and renal proximal convoluted tubule epithelial cells, and the expression in kidney tissue is significantly increased when it is damaged. Research suggests that KIM-1 has good sensitivity and specificity in acute and chronic renal impairment [13]. Some scholars have discovered that for patients undergoing PCI, the rise in urine KIM-1 level has good

Table 3. ROC-AUC for Scr, NGAL and KIM-1 at different time points after PCI.

Time	Item	AUC	95%CI	Sensitivity	Specificity	Threshold point	P
6 h after operation	Scr (umol/L)	0.58	0.46~0.66	63.57	59.34	72.87	0.42
	NGAL (ng/ml)	0.81	0.70~0.88	97.64	67.78	96.35	0.03
	KIM-1 (ng/L)	0.74	0.64~0.82	62.86	90.67	1.12	0.02
12 h after operation	Scr (umol/L)	0.79	0.70~0.86	69.36	82.23	77.68	<0.01
	NGAL (ng/ml)	0.89	0.81~0.95	94.95	76.65	93.93	<0.01
	KIM-1 (ng/L)	0.84	0.76~0.89	66.58	97.36	1.13	<0.01
24 h after operation	Scr (umol/L)	0.86	0.80~0.92	61.59	95.64	72.74	<0.01
	NGAL (ng/ml)	0.89	0.81~0.94	96.63	68.72	97.57	<0.01
	KIM-1 (ng/L)	0.87	0.79~0.92	63.67	90.53	1.08	0.01
48 h after operation	Scr (umol/L)	0.87	0.82~0.94	90.42	74.89	89.03	<0.01
	NGAL (ng/ml)	0.79	0.72~0.85	90.56	68.82	95.59	<0.01
	KIM-1 (ng/L)	0.72	0.64~0.79	61.28	97.50	1.20	<0.01

$P < 0.05$ suggested statistically significant.

predictive value for the diagnosis of early CIN, and has a good predictive value in long-term poor prognosis of CIN. A prospective study in patients with sepsis observed that S_{Cr} began to rise after 24 h after admission, and KIM-1 levels significantly increased after 6 h and reached a peak at 24 h, suggesting that KIM-1 is valuable for the early diagnosis of AKI caused by sepsis [14]. In this study, the AUCs for the serum NGAL and urine KIM-1 were large at 6, 12, and 24 h after PCI. Hence, KIM-1 is a good indicator for the early diagnosis of CIN, while the urine KIM-1 level declines rapidly at 48 h after PCI.

In conclusion, detection of serum NGAL and urine KIM-1 can provide assist in early diagnosis of CIN. In particular, the combined detection of markers such as NGAL and KIM-1 can improve the diagnostic specificity and sensitivity.

However, considering that the occurrence of CIN is affected by multiple factors, the influences of primary disease/age/dose of contrast medium should be discussed. It is known that diabetes is an independent risk factor for CIN. High risk of CIN

development and its prognostic significance in patients with T2DM determine the necessity of individually evaluating the risks for preventive measures during contrast media interventions, which required further research and intensive intervention therapies [15,16]. Weaknesses of the present study include its small sample size and single-center design, and further studies with larger sample sized are needed to assess the roles of serum NGAL and urine KIM-1 in early diagnosis of CIN.

Conclusions

Serum NGAL and urine KIM-1 levels reflect early changes in renal functions, and their combined use for detection is conducive to early diagnosis of CIN.

Conflict of interest

None.

References:

- Powell SP, Chawla R, Bottinor W et al: Race, contrast-induced nephropathy and long-term outcomes after coronary and peripheral angiography and intervention. *Cardiovasc Revasc Med*, 2018; 265: 231–45
- Hossain MA, Costanzo E, Cosentino J et al: Contrast-induced nephropathy: Pathophysiology, risk factors, and prevention. *Saudi J Kidney Dis Transpl*, 2018; 29: 1–9
- Samadian F, Dalili N, Mahmoudieh L, Ziaei S: Contrast-induced nephropathy: Essentials and concerns. *Iran J Kidney Dis*, 2018; 12: 135–41
- Briasoulis A, Pala M, Telila T et al: Statins and contrast-induced nephropathy: A systematic review and meta-analysis. *Curr Pharm Des*, 2017; 8: 7141–48
- Annamalai SK, Kapur NK: Contrast induced nephropathy after coronary or vascular intervention: More biomarkers than answers. *Catheter Cardiovasc Interv*, 2018; 91: 1192–93
- Miah OF, Dowel FA, Latif A et al: NGAL (neutrophil gelatinase-associated lipocalin) is an early predictor of acute kidney injury after cardiac surgery and variation of NGAL values in homogenous study subject. *Mymensingh Med J*, 2018; 27: 212–15

7. Pang HM, Qin XL, Liu TT et al: Urinary kidney injury molecule-1 and neutrophil gelatinase-associated lipocalin as early biomarkers for predicting vancomycin-associated acute kidney injury: A prospective study. *Eur Rev Med Pharmacol Sci*, 2017; 21: 4203–13
8. Corbacioglu SK, Cevik Y, Akinci E et al: Value of plasma neutrophil gelatinase-associated lipocalin (NGAL) in distinguishing between acute kidney injury (AKI) and chronic kidney disease (CKD). *Turk J Emerg Med*, 2017; 17: 85–88
9. Buonafine M, Martinez-Martinez E, Jaisser F: More than a simple biomarker: The role of NGAL in cardiovascular and renal diseases. *Clin Sci (Lond)*, 2018; 132: 909–23
10. Benzer M, Alpay H, Baykan O et al: Serum NGAL, cystatin C and urinary NAG measurements for early diagnosis of contrast-induced nephropathy in children. *Ren Fail*, 2016; 38: 27–34
11. Filiopoulos V, Biblaki D, Lazarou D et al: Plasma neutrophil gelatinase-associated lipocalin (NGAL) as an early predictive marker of contrast-induced nephropathy in hospitalized patients undergoing computed tomography. *Clin Kidney J*, 2013; 6: 578–83
12. Duan SB, Liu GL, Yu ZQ, Pan P: Urinary KIM-1, IL-18 and Cys-c as early predictive biomarkers in gadolinium-based contrast-induced nephropathy in the elderly patients. *Clin Nephrol*, 2013; 80: 349–54
13. Chaykovska L, Heunisch F, von Einem G et al: Urinary vitamin D binding protein and KIM-1 are potent new biomarkers of major adverse renal events in patients undergoing coronary angiography. *Plos One*, 2016; 11: e145723
14. Tu Y, Wang H, Sun R et al: Urinary netrin-1 and KIM-1 as early biomarkers for septic acute kidney injury. *Ren Fail*, 2014; 36: 1559–63
15. Barbieri L, Verdoia M, Schaffer A et al: Pre-diabetes and the risk of contrast induced nephropathy in patients undergoing coronary angiography or percutaneous intervention. *Diabetes Res Clin Pract*, 2014; 106: 458–64
16. Lou B, Gao H: Contrast-induced nephropathy prevention by remote ischemic preconditioning: Effect of diabetes mellitus. *Int J Cardiol*, 2018; 268: 41