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Study of plasma neutrophil gelatinase-associated lipocalin as an early marker of acute kidney injury following contrast agents

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ABSTRACT

Introduction: Acute kidney injury (AKI) is a common illness among hospitalized patients, which increases mortality and morbidity rate. Creatinine and neutrophil gelatinase-associated lipocalin (NGAL) are the most commonly conducted biomarkers of AKI.
Objectives: The aim of current study was to assess NGAL as an early biomarker for AKI diagnosis following contrast agents.
Patients and Methods: To follow the aim of the present case-control research, 165 individuals were entered the study; 80 patients were selected from Valiasr hospital of Zanjan city, and 85 healthy individuals were enrolled voluntarily. There were not any significant differences in sex distribution among healthy subjects. Plasma NGAL and creatinine were measured immediately before and at 12 and 72 hours post-contrast agents' exposure.
Results: There were 89 males and 76 females in the study groups. The mean age was 61.3 ± 18.2 years and 62.1 ± 17.2 years in the intervention and healthy groups, respectively. The mean of serum creatinine and NGAL level were 1.0± 0.2 mg/dL and 63.6 ±23.6 ng/mL in the control and 0.92 ± 0.23 mg/dL and 110 ± 82.3 ng/mL in the case group, respectively. There were remarkable different between serum NGAL and creatinine in the both groups. The NGAL level in the healthy and the patient group were 63.6 ± 23.6 ng/mL and 100.1 ± 121.7 ng/mL, respectively, which was considerably different between the case and control groups ($P=0.01$). The highest level of specificity and sensitivity were 86 and 55.5; they could be the main appropriate options for defining cut off.
Conclusion: The findings showed, that NGAL level is an extremely specific and sensitive indicator for AKI diagnosis after 72 hours. Hence, this approach can open a novel insight into the AKI therapies.

Original

Implication for health policy/practice/research/medical education:
To assess NGAL as an early biomarker for AKI diagnosis following contrast agents, we found that NGAL level is an extremely specific and sensitive indicator for AKI diagnosis after 72 hours. Hence, this approach can open a novel insight into the AKI therapies.

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Introduction

Acute kidney injury (AKI) is the common and potentially devastating disorder of hospitalized patients that increases mortality and morbidity (1-3). AKI frequency varies from about 5% of the entire admitted patients in hospital to approximately 50% of those in intensive care units (ICUs). Despite, considerable progress in discovering the pathophysiologic mechanism of AKI, however several interventions still are needed for better knowledge of this disease (4-6).

The evidence suggests that precise etiology of this failure could be solved by renal biomarkers in the primary stages. Early detection may permit the physicians for timely diagnosis and renal injury treatment, which leads to proper monitoring at the right time and improved mortality rate (7). Evaluating serum and urine creatinine is the major common measure to detect renal failure, despite their identified limitations in current clinical assessment (8).

Serum creatinine concentration showed narrow specificity and sensitivity; particularly, it has a slow rate of change, therefore it is not enough effective in AKI early diagnosis (9). The American Society of Nephrology (ASN) has been suggested more validate and novel indicator of AKI (9, 10).

Neutrophil gelatinase-associated lipocalin (NGAL) is a 25-kD molecule, that releases from renal tubular cells following the nephrotoxic or ischemic insult (11). NGAL level is elevated in several clinical settings of AKI, including patients receiving intravenous contrast media (ICM) infusion for coronary angiography (12), patients admitted to the emergency room (13) or after coronary surgery (14). Some evidences reported, that urine and plasma/serum NGAL could be as a novel biomarker for AKI assay to evaluate the duration and severity of renal injury (15, 16).

In vitro studies demonstrated, that NGAL messenger RNA and molecules originating from the renal are always increased, and probably could be detected in the murine urine in the early phase of AKI (after 1-3 hours) (17, 18). Further, a previous cohort report indicated that NGAL level is extremely associated with septic as well as non-septic AKI in ICU patients (19).

Objectives

In the current study, we aimed to clarify the possible relation of NGAL concentration after ICM infusion in admitted patients of Zanjan province in Iran.

Patients and Methods

Study design

The present case-control research study consisted of 80 patients, who had been admitted in Valiasr hospital of Zanjan during 2017-2018. The patients received contrast agents in computerized tomography (CT) scan process randomly. RIFLE (risk, injury, failure, loss, and end stage renal disease) criteria have been considered as AKI. Exclusion criteria included patients with a history of renal tumors, renal infection and history of several antibiotics administration, nephrotoxic (aminoglycosides) and the interfering drugs in creatinine measurement (trimethoprim sulfamethoxazole) before or during the study period.

Patients' demographic information including age, gender, history of any illnesses including blood pressure and diabetes mellitus, heart disease and history of renal insufficiency were collected by questionnaires. Subsequently, patient's peripheral blood samples were obtained and the serum was separated.

Procedures

The patient's peripheral blood samples were collected again after 12 hours using contrast agents to determine NGAL and creatinine plasma levels. Subsequently, three days (72 hours) later, the sampling was performed to re-assay plasma creatinine. It should be noted, that in this study, the nephropathy of contrast agents was defined as either a 25% raise in serum creatinine from baseline or a 0.5 mg/dL rise in total serum creatinine, during 48-72 hours following intravenous contrast administration or requiring dialysis within a week (20).

Enzyme-linked immunosorbent assay

The NGAL plasma level was determined using the ELISA kit (Cristal Day Biotech Kit; China) according to the manufacturer's protocol.

Statistical analysis

Data were analyzed using SPSS 21.0 version software package (Inc; Chicago, IL). Data were studied by independent sample *t* test and one-way ANOVA, as well as Tukey's post hoc test. Further, Mann-Whitney U (Wilcoxon rank) or Spearman's correlation tests was conducted to study the correlation of continuous variables without normal distribution. Data distribution was also performed by Kolmogorov Smirnov test. *P* value less than 0.05 was considered significant.

Results

Enrolled cases

From overall 165 individuals, there was not any considerable differences in sex distribution among healthy individuals. Among controls, 44 (51.8%) individuals were male and 41(48.2%) were female. In the patient group 45 (56.3%) out of 80 patients were male and rest of them were female 35 (43.8%).

Mean age of patients in the intervention and control groups were 61.3 ± 18.2 and 62.1 ± 17.2 years, respectively. Seventy-five (88.2%) individuals of the control group, and 71 individuals (88.2%) of the intervention group did not have diabetes. Total number of patients with

hypertension was 57 (67.1%) in the control group, and 50 (62.5%) in the intervention group. In addition, 63 cases (74.1%) of the control group and 58 cases (72.5%) of the intervention group had heart disease. Eight (9.4%) subjects of the control group and 8 patients (10.0%) of the intervention group used non-steroidal anti-inflammatory drugs. The angiotensin-converting enzyme inhibitors and angiotensin ii receptor blockers drugs were rarely used in both groups (Table 1).

The mean of serum creatinine and NGAL level were 1.0 ± 0.2 mg/dL and 63.6 ± 23.6 ng/mL in the control and 0.92 ± 0.23 mg/dL and 110 ± 82.3 ng/mL in the patients group respectively. Twenty (15%) out of 80 patients in the intervention group suffered from AKI. In AKI patients, the serum creatinine was 0.9 ± 0.27 mg/dL before intervention; it was also 1.0 ± 0.23 mg/dL and 1.3 ± 0.44 mg/dL 12 and 72 hours after intervention, respectively. In non-AKI group, creatinine level was 0.92 ± 0.24 mg/dL before intervention, and 0.89 ± 0.18 mg/dL and 0.82 ± 0.15 mg/dL after 12 and 72 hours, respectively (Table 2).

According to the Table 3, there were significant differences in 72-hour creatinine between the two groups of AKI and non-AKI ($P=0.001$). The NGAL levels in the AKI and the control group were 121.7 ± 100.1 ng/mL and 63.6 ± 23.6 ng/mL, respectively; this difference was statistically significant ($P=0.01$; Table 4).

Figure 1 shows the sensitivity and specificity of NGAL level to set cut off for AKI occurrence prediction after intervention. According to the analysis, the highest level of sensitivity and specificity were 55.5 and 86; it can be the most suitable option for cut off determination. Based on *t* test study, there was no significant correlation between AKI and 12-hour serum creatinine with these P values, however there was a remarkable association with 72-hour creatinine.

Discussion

The serum creatinine level is an inadequate biomarker of renal dysfunction. The glomerular filtration rate (GFR) could show great losses earlier than creatinine evaluation. In addition, serum creatinine levels need more than a few days to reach the steady state to indicate renal injury. More precise techniques, including radiotracer clearances has

Table 1. Patient and control group's characteristics

Clinical characterize		Control (n %)	Patients (n %)	*P* value
Gender	Male	44 (51.8)	45 (56.3)	0.56
	Female	41 (48.2)	35 (43.8)	
Age (y)		62.1±17.2	61.3±18.2	0.62
Diabetes	No	75 (88.2)	71 (88.8)	0.91
	Yes	10 (11.8)	9 (11.3)	
Hypertension	Yes	57 (67.1)	50 (62.5)	0.62
	No	28 (32.9)	30 (37.5)	
Kidney injury	Yes	84 (98.8)	78 (97.5)	0.61
	No	1 (1.2%)	2 (2.5)	
Heart disease	Yes	63 (74.1)	58 (72.5)	0.81
	No	22 (25.9)	22 (27.5)	
NSAID used	Yes	77 (90.6)	72 (90.0)	0.62
	No	8 (9.4)	8 (10%)	
ARBs Used	Yes	82 (96.5)	75 (93.8)	0.41
	No	3 (3.5)	5 (6.3)	
ACEI used	Yes	84 (98.8)	78 (97.5)	0.52
	No	1 (1.2)	2 (2.5)	

Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; NSAIDs, Non-steroidal anti-inflammatory drugs.

Table 2. The creatinine and NGAL levels in the patient and control groups

Variable	Control (Mean ± SD)	Patients (Mean ± SD)	*P* value
Creatinine (mg/dL)	1±0.2	0.92 ±0.23	0.05
NGAL (ng/mL)	63.6±23.6	110±82.3	0.001

NGAL, neutrophil gelatinase-associated lipocalin.

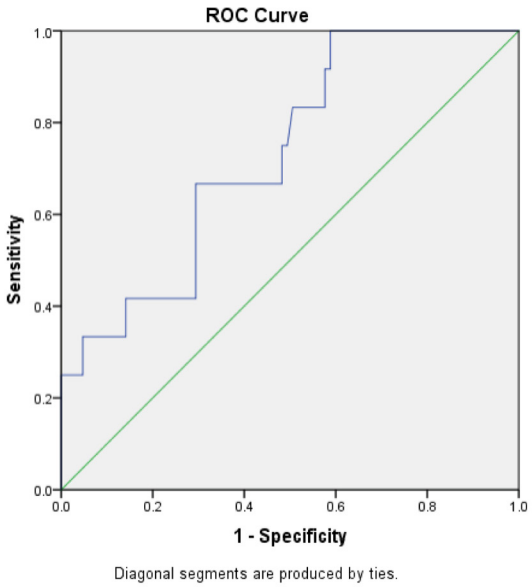

Figure 1. Linear diagram of the sensitivity and specificity of the NGAL level.

Table 3. The mean of measured variables in the two groups of AKI and non-AKI patients

Variable	Non-AKI (Mean ± SD)	AKI (Mean ± SD)	*P* value
Creatinine before contrast (mg/dL)	0.92±0.24	0.9 ± 0.27	0.886
Creatinine after 12 h (mg/dL)	0.89±0.18	1±0.23	0.058
Creatinine after 72 h (mg/dL)	0.82±0.15	1.3 ± 0.44	0.001

AKI, acute kidney injury.

Table 4. Comparison of NGAL mean between AKI and control group

NGAL	Control		AKI		*P* value
	Median	Mean (SD)	Median	Mean (SD)	
	67.2 (40.8)	63.6 (23.6)	78.4 (58.2)	121.7 (100.1)	0.01

NGAL, Neutrophil gelatinase-associated lipocalin; AKI, Acute kidney injury.

radiation and are more invasive; they also need more time to be performed.

In the current study, the plasma NGAL has correlation with serum creatinine level in 80 studied patients in hospital of Zanjan city. In this study, the mean serum creatinine was 0.9 ± 0.27 g/dL before intervention; it was 1.0 ± 0.23 mg/dL and 1.3 ± 0.44 mg/dL in the AKI patients after 12 and 72 hours of intervention. Similarly, in a group of patients, who did not have AKI, the mean serum creatinine was 0.92 ± 0.22 mg/dL before intervention; it was 0.89 ± 0.18 after mg/dL 12 hours of intervention. There was a significant relation between the two groups ($P = 0.001$; Table 3). As the results shown, contrast agents can increase the serum creatinine level in AKI patients at least three days following administration of contrast medium. Hence, serum creatinine level could not be a valid biomarker in the early stage of AKI.

In this study, serum creatinine levels were statistically significant at three-time intervals. Although, there were changes in serum creatinine level, it cannot be conducted clinically to predict the function of the kidney after exposure to the contrast agent.

In our study, the NGAL level in the AKI patients and the control group were 121.7 ± 100.1 ng/mL and 63.6 ± 23.6 ng/mL. There was significant relation in both groups ($P = 0.01$). Figure 1 shows the sensitivity and specificity of the NGAL level as a cut off to predict AKI occurrence after intervention. According to the analysis, 55.5 % sensitivity and 86 % specificity can be the most suitable options for cut off determining.

Padhy et al indicated, that the serum NGAL level was more than primary level after 4 hours of the procedure, and then slowly decreased to the usual level after 48 hours in AKI patients. They suggested, that NGAL and cystatin C could perform as the primary indicator of contrast-induced AKI in patients undergoing selective coronary intervention. Further, hypertensive patients are at risk to increase contrast-induced AKI (21).

Russell et al confirmed, that NGAL could be as trigger immediate intervention. They showed, that NGAL is a novel biomarker of contrast-induced nephropathy in pediatrics for AKI patient monitoring. NGAL assessment in early stage avoids utilizing of other nephrotoxins, and improves renal perfusion to decrease more damages (22). Reviewing others reports showed that NGAL could be involved as the predictive marker in acute renal failure. Plasma NGAL (sensitivity = 100%, specificity = 92%; cut-off value = 309 ng/mL) is an extremely sensitive and particular prognostic biomarker compare to serum creatinine (sensitivity = 66.7%, specificity = 61.9%) on the first day after renal transplantation. Our results highlighted the importance of timely evaluation of plasma NGAL as a predictive indicator (23).

A previous report indicated that serum NGAL stage is an efficient indicator in renal injury in brucellosis patients, who used gentamycin. No considerable difference was found between NGAL levels before and after gentamicin receiving (P value = 0.82). They suggested, that NGAL assessment should be performed by more sensitive and specific kits in larger population. Wan et al confirmed the renal injury by serum creatinine evaluation only 12-48 hours following cardiac surgery. In addition, urine NGAL levels significantly increased in acute renal failure patients after 2-4 hours. They introduced serum/urine NGAL level as powerful predictor of AKI (24).

Conclusion

Our study indicated, that evaluating serum NGLA was significantly correlated with AKI following contrast agents. It is potential, that serum NGAL could provide a specificity and full sensitivity screening tool for AKI early diagnosis. Therefore, this approach could open a new window for AKI therapeutic agents.

Limitations of the study

Evaluating serum and urine creatinine is the major common measure to detect renal failure, despite their identified limitations in current clinical assessment.

Authors' contribution

Conceptualization: AP.
Methodology: SG, AP.
Validation: AP.
Formal analysis: KK.
Investigation: SMM.
Resources: AE.
Data curation: SG, AP.
Visualization: SMM.
Supervision: AP.
Project administration: AP.
Writing–original draft preparation: NP.
Writing–review and editing: NP.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The Ethics Committee of Zanjan University of Medical Sciences approved this study (Ethical code #IR.ZUMS.REC.1394.03). Accordingly, written informed consent was taken from all participants before any intervention. Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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