Research Paper Serum Neutrophil Gelatinase-associated Lipocalin: A Biomarker of Renal Impairment in Hypertensive Patients

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ABSTRACT

Background and Aim: Hypertension is one of the leading causes of chronic kidney disease (CKD). Neutrophil gelatinase-associated lipocalin (NGAL) is a novel and sensitive biomarker in acute and chronic renal injury. The present study investigated serum and urinary NGAL as markers of kidney damage in hypertensive and CKD patients.

Materials and Methods: This case-control study was performed on 28 hypertensive patients, 28 patients with CKD, and 33 healthy volunteers. Serum and urinary NGAL levels were measured using the ELISA method. Creatinine and urea concentrations were measured by the routine methods. Receiver-operating characteristic (ROC) curve analysis was employed to find the best serum and urinary NGAL cut-off values for detecting renal function.

Results: Both serum and urinary NGAL levels were higher in CKD patients than in hypertensive patients and healthy controls (serum NGAL: 193.48±50.62 vs 99.47±26.65 and 48.74±12.07, P<0.001; urinary NGAL: 63.78±16.54 vs 23.24±6.87 and 11.36±3.4, P<0.001 respectively). There was a significant positive correlation between serum and urinary NGAL with serum urea and creatinine. Serum and urinary NGAL levels showed a significant inverse correlation with the estimated glomerular filtration rate. In ROC analysis, serum NGAL had the best diagnostic profile with an AUC of 0.938 (95% CI: 0.865–0.978) and the best cut-off value of 64.61 ng/mL (sensitivity 97.73%; specificity 77.27%.

Conclusion: These results revealed that serum NGAL is a reliable marker for early diagnosis of renal injury in hypertensive patients.

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1. Introduction



ypertension is a major public health problem in many countries and one of the causes of premature death. Approximately one in four adults have hypertension, and it is predicted that this number will escalate to more than 1.56

billion by 2025 [1]. Nearly two-thirds of people with hypertension live in low- and middle-income countries, resulting in a substantial economic burden for these countries [1]. High blood pressure is one of the risk factors for chronic kidney disease (CKD), which can be both a cause of kidney disease and a symptom of kidney disease. CKD has become a serious public health issue and one of the leading causes of mortality and morbidity in the world [2].

Based on the World Health Organization estimates of mortality and disease burden, CKD will rank the 13th leading cause of death in 2030 compared to the 17th in 2002 [2]. CKD causes progressive and irreversible kidney structure impairment and markedly decreases the glomerular filtration rate (GFR) [3]. Early diagnosis of CKD is an essential step for regression of kidney failure, its subsequent complications, morbidity, and mortalities. Currently, the diagnosis of CKD is usually based on measuring blood urea nitrogen levels and serum creatinine (sCr). However, sCr cannot be considered an ideal biomarker for estimating kidney injury because there is no linear relationship between sCr and the estimated glomerular filtration rate (eGFR). Also, it is insensitive, and factors like age, muscle mass, gender, and medications can affect it. The creatinine level increases in serum only when 40%-50% of kidney function is lost [4-6]. This limitation may miss kidney impairment in the early stages of CKD and therefore, delays accurate diagnosis and implementation of therapeutic interventions. Neutrophil gelatinase-associated lipocalin (NGAL), also known as siderocalin, is a glycoprotein (25 kd) that is released from renal tubular cells in response to various injuries to the kidney [7, 8].

NGAL is one of the most promising biomarkers for early detection of acute kidney injury (AKI) [9, 10]. Numerous studies have also defined the role of NGAL in chronic kidney disease and have shown associations between higher urinary and blood NGAL levels and progression of CKD [11-14]. In this study, we assessed serum and urinary NGAL levels in hypertensive patients and CKD and then compared its diagnostic power with sCr.

2. Materials and Methods

This case-control study was conducted on patients referred to Kamkar-Arabnia Hospital affiliated with Qom University of Medical Sciences in Qom City, Iran. A total of 28 hypertensive patients (systolic blood pressure \geq 140 mm Hg and diastolic blood pressure \geq 90 mm Hg) aged 35-70 years were included in this study. A doctor confirmed high blood pressure in these patients on at least two separate occasions. To minimize potential confounding factors in this group, patients with chronic diseases, such as infection, malignancy, cardiovascular disease, liver disease, or elevated serum creatinine and urea, were excluded from the study. Finally, 28 patients with CKD and 33 healthy volunteers were recruited. The healthy population consisted of samples from those who visited the hospital for periodic medical checkups and proved to have no specific clinical or laboratory problems. The inclusion criteria were the presence of CKD in stages 3-5 according to the National Kidney Foundation's classification and using the Cockcroft-Gault formula, which was verified by the serum creatinine measurement and the physician's approval. We excluded patients under hemodialysis, those with liver disease, infectious disease, malignancy, and acute kidney problems. Demographic and clinical data regarding age, gender, and so on were obtained.

This study was approved by the Ethics Committee of Qom University of Medical Sciences, and written informed consent was acquired from all participants before the study. Blood samples were taken from patients in the morning and subsequently centrifuged at 2500-3000 rpm for 10 min at 4°C. Then, the sera were aliquoted and stored at -80°C for batch analysis. Morning spot urine samples were collected from patients and then centrifuged at 4°C for 10 min at 5000 rpm to remove particulate matter, and cell debris and the supernatants were stored in aliquots at -80°C until further analysis. The serum and urine concentration of NGAL was measured using a commercially available sandwich-type Enzyme-Linked Immunosorbent Assay (ELISA) kit (ZellBio), in accordance with the manufacturer's instructions. Briefly, microtiter plates pre-coated with an antibody specific to NGAL were incubated with samples or standards. Then, biotinylated NGAL antibody and avidin-Horseradish peroxidase (HRP) conjugate were added to the wells. Then, the substrate solution was added to each well.

A stop solution terminates the enzyme-substrate reaction. Finally, NGAL concentration was measured at 450 nm wavelength by the microplate reader. All measurements were made in a duplicate and blinded manner. A standard curve was created by plotting absorbance value versus NGAL concentration of standards, and concentrations of unknown samples were determined using this standard curve. Serum urea and serum creatinine (sCr) were measured according to standard methods in the routine clinical laboratory. The estimated glomerular filtration rate (eGFR) was calculated using a Cockcroft-Gault formula:

eGFR (mL/min)=[(140–Age)×body weight (kg)/72×sCr (mg/dL)]×(0.85 if female)

Statistical analysis

Statistical analyses were performed in SPSS software (version 19.0, SPSS Inc, Chicago, Ill, USA) and MedCalc version 15.8 (MedCalc Software, Ostend, Belgium). Continuous variables are expressed as the mean±SD. The Pearson correlation coefficient (r) was used to investigate the correlation between serum NGAL (sNGAL) and urinary NGAL (uNGAL) and the other clinical variables. Differences among groups were tested with a 1-way analysis of variance and Bonferroni post-hoc test. The χ^2 test was used for comparing qualitative data. Receiver-operating characteristics (ROC) curve analysis was used to assess and compare the diagnostic accuracy of serum and urinary NGAL for identifying the patients at risk of CKD. In all cases, P≤0.05 were considered statistically significant.

3. Results

Overall, 89 participants were included in these analyses and completed the present case-control study. Their demographic, clinical, and laboratory characteristics are summarized in (Table 1). The study participants were 28 hypertensive patients (14 women and 14 men; Mean±SD age: 58±10.66 years), 28 patients with CKD (10 women and 18 men; Mean±SD age: 62.53±6.89 years), and 33 healthy volunteers (16 women and 17 men; Mean±SD age: 50.39±8.34 years). The results of the χ^2 test showed no significant difference among the three groups regarding sex and age. Serum urea and creatinine concentrations were higher in CKD patients than in hypertensive and healthy subjects, and this difference was significant. For all subjects in the hypertensive and control group, serum urea and creatinine levels were in normal ranges. Systolic (SBP) and diastolic blood pressure (DBP) values were significantly higher in the hypertensive and CKD groups as compared with the control group (SBP: 157.88±14.29 and 135.7±18.7 mm Hg vs 117.5±9.8 mm Hg, P<0.001; DBP: 92.8±5.2 and 83.9±6.8 mm Hg vs 79.1±4.1 mm

Hg, P<0.001, respectively). Additionally, GFR values were significantly lower in the CKD group compared to the hypertensive patients and control group (33.85±13.02 and 87.72±12.63 vs 99.73±7.06 mL/ min/1.73 m², P<0.001) (Table1). sNGAL and uNGAL concentrations were significantly higher in the CKD group compared with the hypertensive and healthy subjects, and this difference was significant. The Pearson test analysis revealed that sNGAL correlated positively with serum urea (r=0.647, P<0.001), sCr (r=0.631 P<0.001), and uNGAL (r=0.806, P<0.001), but correlated negatively with eGFR (r=-0.771, P<0.001) (Figure 1). sNGAL level correlated significantly but weakly with SBP (r=0.266, P=0.013). There were no significant correlations between sNGAL and DBP. Also, uNGAL displayed a highly significant correlation with serum urea and sCr levels (r=0.786, P<0.001 and r=0.794, P<0.001, respectively). A negative correlation was found between uNGAL and GFR (r=-0.875, P<0.001) (Figure 1). The results demonstrated no significant correlations between uNGAL and systolic and diastolic blood pressure (Table 1, Figure 1).

ROC curve analysis was performed to define the diagnostic value of sNGAL and uNGAL for detecting impaired renal function. The GFR determined with the Cockcroft-Gault formula was used as the reference. The area under the curve (AUC) was 0.938 (95% CI: 0.865 to 0.978) for sNGAL with a best cutoff value of 64.61 ng/mL (sensitivity 97.73%; specificity 77.27%). This is followed by uNGAL, showing an AUC of 0.895 (95% CI: 0.812–0.950) and the best cutoff value of 18.32 ng/mL (sensitivity 90.91%; specificity 81.82%). The AUC was 0.905 (95% CI: 0.823–0.957] for sCr and 0.904 (95% CI: 0.822–0.957) for serum urea. The comparison of the AUCs indicated that the diagnostic accuracy of sNGAL was significantly more than those of SCr, serum urea, and uNGAL (Figure 2).

4. Discussion

High blood pressure is one of the primary risk factors for chronic kidney disease [15]. CKD is a major public health problem in many countries. The disease is associated not only with mortality but also with considerable morbidity and disability. CKD is usually asymptomatic in the early stages [16]. Given its asymptomatic nature, early diagnosis of this disease is an important step in preventing CKD complications. Hypertension is a wellknown risk factor for CKD that can produce functional and structural renal impairments. Currently, detection of CKD is usually based on the levels of serum creatinine, blood urea nitrogen, and eGFR. However, these

Variables	Mean±SD		
	Healthy Control	Hypertensive	Chronic Kidney Disease
Age (y)	50.39±8.34	58±10.66	62.53±6.89
Weight (kg)	73.81±14.06	77.34±10.26	75.46±15.11
Systolic *# &	11.75±0.98	15.78±1.42	13.57±1.87
Diastolic *# &	7.91±0.41	9.28±0.52	8.39±0.68
sCr *&	0.80±0.10	0.84±0.12	2.22±0.83
sUrea*&	35.14±5.6	36.47±8.30	87.08±29.58
eGFR*# &	99.73±7.06	87.72±12.63	33.85±13.02
sNGAL*# &	48.74±12.07	99.47±26.65	193.48±50.62
uNGAL*# &	11.36±3.4	23.24±6.87	63.78±16.54
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Table 1. Demographic and clinical characteristics of the different study groups

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CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; NGAL: neutrophil gelatinase-associated lipocalin. *P<0.05 for healthy controls and CKD group; #P<0.05 for healthy controls and hypertensive group; & P<0.05 for CKD group and

Hypertensive group.

measures are imprecise and relatively insensitive to small changes in renal function and influenced by various extrarenal factors. Therefore, there is concern about strategies for early detection of kidney damage in patients at risk of CKD. Currently, researchers are seeking new biomarkers that can reflect early kidney injury and thus provide a window for early clinical intervention. Recently, NGAL has been suggested as a new sensitive biomarker for the early diagnosis of acute and chronic kidney disease [17, 18].

In this study, we evaluated the clinical usefulness of measuring sNGAL and uNGAL as early markers of reduced GFR in patients with CKD and hypertension. We compared these results with those of sCr and eGFR. Reference values of sNGAL and uNGAL must be established for routine use in clinical practice, particularly in the early stages of CKD, when therapeutic interventions are most effective. In the present study, higher sNGAL and uNGAL concentrations were identified in CKD patients compared to those in the hypertensive and healthy groups.

In line with the present results, several studies have demonstrated that NGAL level is significantly higher in patients with CKD than in healthy individuals [3, 19]. However, both sNGAL and uNGAL levels were higher in hypertensive subjects than in the control group and lower than CKD group. In the study by Gökhan Aksan et al., sNGAL concentrations were found to be significantly higher in the non-dipper and dipper hypertension groups compared with the control group (84.9 ± 23.0 ng/mL and 62.1 ± 17.8 vs 46.6 ± 13.7 ng/mL, P<0.017, respectively) [20]. The values of sNGAL obtained by Faranak Kazerouni et al. in hypertensive patients and healthy volunteers were 124.54 ± 118.67 ng/mL and 14.59 ± 3.71 ng/ mL, respectively [21]. These values were similar to the values of our study. In the present study, both sNGAL and uNGAL were negatively correlated with eGFR and positively correlated with sCr and serum urea.

Similar to our results, in the study by Bolingano et al., serum and urinary NGAL were significantly higher in CKD patients than in controls, and both showed a significant positive correlation with sCr and a significant negative correlation with GFR [22]. In Malyszko's study, hypertensive patients had significantly higher NGAL than normotensives, and sNGAL showed a statistically significant positive correlation with sCr, serum urea, uNGAL, and a significant negative correlation with calculated GFR [23]. These results, like previous studies, confirm the relationship between sNGAL concentration and renal dysfunction. We found that sNGAL levels are positively correlated with SBP, but no correlation was observed between serum sNGAL and DBP. In the study by Carmen A. Peralta et al., serum cystatin C as a marker of renal function was significantly and linearly associated with SBP but not with DBP [24].



Figure 1. Correlation Between A) sNGAL and eGFR, B) uNGAL and eGFR



eGFR: estimated glomerular filtration rate; sNGAL: serum neutrophil gelatinase-associated lipocalin; uNGAL: urine neutrophil gelatinase-associated lipocalin.

Recently, Mori et al. suggested the "forest fire theory," which might explain the relationship between NGAL and GFR. According to this theory, a rise in serum creatinine is the passive result of loss of kidney function, but the increase of NGAL in renal injury is not just a result of decreased clearance. This hypothesis assumes that the increase in NGAL in kidney disease results from a sustained production by inflamed but vital tubular cells. Although NGAL could be produced systemically by neutrophils/macrophages or inflamed vasculature, it is frequently found in hypertension and chronic kidney disease [25]. Because NGAL is increased in atherosclerotic plaques, it might also be released into the circulation from inflamed endothelium in patients with hypertension. Therefore, the source of serum NGAL during renal injury could be a complex from the injured tissues (renal injury) and circulation. However, the correlation coefficient may show only a linear association but cannot always determine the diagnostic accuracy of a test.

The best method for the evaluation assessment of diagnostic accuracy of a test is ROC analysis. Accord-





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Figure 2. Receiver-Operating Characteristics (ROC) curves of serum Neutrophil Gelatinase Associated Lipocalin (NGAL), serum urea, serum creatinine, and urinary NGAL

ing to the AUC values, sNGAL and uNGAL showed a very good diagnostic profile. Based on the study results, the best cut-off value for sNGAL and uNGAL to predict early stages of CKD were 64.61 ng/mL (sensitivity, 97.73%; specificity, 77.27%) and 18.32 ng/mL (sensitivity, 90.91%; specificity, 81.82%), respectively. In the A. Kaul et al. study, ROC curve analyses were performed to define the diagnostic value of sNGAL and uNGAL in identifying diabetic nephropathy. Based on the study results, the best cut-off value for serum and urinary NGAL were 78.73 ng/mL (sensitivity, 95.1%; specificity, 100.0%) and 21.31 ng/mL (sensitivity, 95.1%; specificity, 100%), respectively [26]. In another study, the diagnostic value of serum and urinary NGAL in chronic kidney disease was investigated. The best cut-off level was 435 ng/mL (sensitivity, 83.9%; specificity, 53.8%) for serum NGAL and 231 ng/mL (sensitivity, 80.6%; specificity, 73.8%) for urinary NGAL. The cut-off value in our study is much lower than this investigation [22]. In a study by Faranak Kazeroun et al., the best cut-off value for plasma NGAL to predict early stages of CKD was 32.2 ng/mL with a sensitivity of 96% and specificity of 100%. These results are similar to those obtained in the present study [21]. In a study by A. Kaul et al., the best cut-off values to predict early stages of kidney disease for plasma NGAL was \geq 32.2 ng/mL (sensitivity

and specificity were 96% and 100%) [26]. Although the results of our study suggest that serum NGAL may be a potential biomarker for CKD in hypertensive patients, future studies are mandatory to clarify our findings.

The current study has some limitations. First, the relatively small sample size of the study limits the precision of the results. Second, due to the cross-sectional design of our study, we cannot determine causality. Specifically, we cannot discern the extent to which kidney dysfunction leads to hypertension or hypertension leads to kidney dysfunction. Third, a short-term observational period with only one point measurement of serum and urinary NGAL and two measurements of Blood pressure restricts the power of conclusions. In summary, we conclude that serum NGAL level might be a valuable marker of renal function in hypertensive patients.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of Qom University of Medical Sciences) IR.MUQ. REC.1395.90).

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Authors' contributions

All authors equally contributed to preparing this article

Conflict of interest

The authors declared no conflict of interest.

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