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Original Article

SERUM NEUTROPHIL GELATINASE-ASSOCIATED LIPOCALIN (NGAL) AS A PREDICTIVE BIOMARKER OF KIDNEY INJURY IN RENAL TRANSPLANTED PATIENTS and CHRONIC KIDNEY DISEASE

ZAINAB A. A. AL-SHAMMA[1], NAHLA GHANIM ALKLYALI[2], INTESAR YOUSIF ALANI[3]

[1]Department of Clinical Pharmacy and Therapeutics. Baghdad College of Pharmacy, Baghdad, Iraq, [2]Educational laboratories, Ministry of Health Baghdad, Iraq, [3]Renal Transplant Center, Medical City, Ministry of Health Baghdad, Iraq
Email: z.alshamma@gmail.com

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ABSTRACT

Objective: Neutrophil gelatinase-associated lipocalin has emerged as a promising biomarker of kidney injury better than creatinine to early predict the acute kidney injury in both chronic kidney diseases and early diagnosis of kidney allograft dysfunction.

Methods: Neutrophil gelatinase-associated lipocalin was evaluated as a new biomarker for acute renal injury in 69 patients were divided in two groups chronic kidney disease patients (stage5), (n=34), and renal transplant patients, (n=35) comparing with apparently healthy control (n= 35) of matching age and weight. Neutrophil gelatinase-associated lipocalin, hsCRP and Cystatin-C were measured by enzyme-linked immune sorbent assay which is included first incubating the test serum in an antigen-coated polystyrene plate, then enzyme labelled anti-immunoglobulin is added and the enzyme then remaining in plate after washing provides a measure of the amount of specific antibody in the serum and in the final step a substance is added that the enzyme can convert to some detectable signal, most commonly a color change in a chemical substrate.

Results: There was a significant increase in serum NGAL of renal transplantation patients, and CKD patients (stage5) than in healthy control subjects (455±145 ng/ml *vs.* 296.4±83.5 ng/ml 486±153 ng/ml vs296. 4±83.5 ng/ml) respectively. A high serum Neutrophil gelatinase-associated lipocalin is noted in renal transplanted patients after one month, then after six months (480±188ng/ml *vs.* 409±78ng/ml). There was a significant negative correlation between serum Neutrophil gelatinase-associated lipocalin in renal transplanted patients, and chronic kidney disease patients (stage 5) with an estimated glomerular filtration rate ($p<0.05$).

Conclusion: Serum neutrophil gelatinase-associated lipocalin seems to be an early predictor of kidney injury and post-transplantation management, including dialysis and grafting function of the kidney.

Keywords: Neutrophil gelatinase-associated lipocalin, Kidney injury, Kidney transplant recipients, Chronic kidney disease

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INTRODUCTION

Acute kidney injury (AKI) is a term that has largely replaced the older term acute renal failure, and is characterized by a rapid decline in the glomerular filtration rate (GFR) resulting in the retention of metabolic waste products, like urea and creatinine and big changes in fluid, electrolyte and acid-base homeostasis Staging of Chronic kidney disease (CKD) is important not only for proper evaluation and treatment but also to consider the need for dialysis. Different comorbid conditions are responsible for the progression of the disease [1]. Since the AKI syndrome is asymptomatic, therefore, its diagnosis is based on functional biomarkers such as serial serum creatinine measurements and renal biopsy, which are routinely used, and considered as gold standard biomarkers of kidney function and for the evaluation of renal allografts [2, 3]. However, creation does not detect an injury or dysfunction early enough to use urgently appropriate therapeutic treatment [2]. In addition, serum creatinine, glomerular filtration rate (GFR), proteinuria measurements, and biopsy remain the current gold standards for the evaluation of renal allografts, though these tests have significant limitations in predicting the immune tolerance or immune-mediated graft loss, and assisting in the management of long-term immunosuppression in renal transplantation patients [4]. Recently, many novel biomarkers have been identified. One of the most promising novel biomarker, namely neutrophil gelatinase-associated lipocalin (NGAL), which is the surrogate marker of renal allograft outcome and a biomarker of acute and chronic graft injury in addition to cystatin-c [5, 6]. NGAL is a promising biomarker for early diagnosis of AKI. NGAL belongs to the lipocalin family. Human NGAL was originally identified as a novel protein isolated from secondary granules of human neutrophils [7]. It is a 25 kDa protein covalently bound to neutrophil gelatinase, whose expression is markedly induced in injured epithelial cells, including kidney, colon, liver and lung [8, 9]. Many preclinical animal studies showed that NGAL up-regulating gene, and protein in the kidney very early after acute injury in animal models [10, 11]. In addition to a number of studies considered that NGAL as a potential biomarker in human AKI [2-4]. Delayed graft function (DGF) is one of the most important complications of kidney transplantation which leads to AKI. This results in increased the risk of acute rejection episodes and decreased long-term survival [12, 13]. Clinical studies investigating NGAL as a biomarker for DGF include data from 1079 patients after renal transplantation [14-16]. The plasma creatinine measurement cannot differentiate between normal renal function, AKI, chronic kidney disease (CKD), and transient azotemia with dehydration. The rise in plasma creatinine concentration, which following an acute injury, is delayed by several hours to days, precluding the timely institution of potential therapies. The NGAL fulfils many of the characteristics important for a useful AKI biomarker. NGAL represents a significant component in the pathophysiology of the disease [17, 18]. Furthermore, NGAL incrementally adds value to the baseline clinical risk assessment, potentially enabling physicians to intervene early to limit the extent of renal injury [19].

The objective of the study was to evaluate serum Neutrophil gelatinase-associated lipocalin as a new predictive biomarker for early diagnosis of acute kidney injury in kidney transplantation patients.

MATERIALS AND METHODS

Subjects

This study included CKD patients (stage 5), (n=34) (12 females, 22 males), and renal transplant patients (RT) (n=35) (10 females, 25

males). The range of age was between 30-60 y. They were from Kidney disease and Transplantation Unit at Baghdad Teaching Hospital during the period from November 2015 to May 2016. The study also included apparently healthy control (n= 35) of matching the age and weight (18 females, 17 males). All procedures on human subjects included in this research were performed after approval from the Ethics Committee of researchers in the Baghdad college of pharmacy/Iraq (NO 97, date 10/1/2017).

Methods

After overnight fasting, 10 ml of venous blood were withdrawn from both patients and controls and collected in a plain tube. At room temperature, and after 30 min, the samples were clotted then centrifuged at 3000 RPM for 15 min. The separated serum was divided into aliquots and stored frozen at (-20 ˚C) to be used later for NGAL, hsCRP, cystatin-c determination of enzyme-linked immune sorbent assay (ELISA). Immediately after separation of the serum, blood glucose, urea and creatinine analysis were done. From CKD-EPI Calculator-four variables MDRD CKD-EPI equation with SI Units using standardized serum creatinine, age, race, gender, white or another race male the estimated glomerular filtration rate was calculated [20]. Body mass index was calculated as body weight (in Kg/Sq height (meter) [21].

Statistical analysis

All values were expressed as mean±standard deviation (mean±SD). All Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS version23. 0). Independent student t-test was performed to assess differences between two means. The Pearson correlation coefficient was used to determine the correlation between quantitative data. P value<0.05 was considered significant.

Table 1: Comparison between serum variables in renal transplanted patients (RT) and their controls as (mean±SD)

Parameter	(RT) Patients (n= 35)	Control(n=34)	P value
NGAL (ng/ml)	455±145	296.4±83.5	<0.0001***
hsCRP (µg/ml)	5.9±3.2	1.24±0.67	<0.0001***
Cystatin-c (ng/ml)	7.1±1.9	5±1.45	<0.0001***
eGFR (ml/min/1.73 m^2)	82.3±31.1	126.1±33.6	<0.0001***
FSB (m. mol/l)	5.5±0.78	5.4±0.78	>0.05
Urea (m. mol/l)	22.1±10.7	10.3±1.7	<0.0001***
Creatinin (µmol/l)	135.9±57.9	68±10.6	<0.0001***

*p<0.05, ** p<0.01, *** p<0.0001, There are no significant differences in age (years) and BMI (kg/m2) between renal transplanted patients, and a control group (34±9. 0 vs 38.0±11), (25.1±2.8vs 26.1±3.4) (p>0.05), while there are significant differences in other biochemical parameters except for glucose (table 1).

Table 2: Comparison between serum variables in CKD (stage5) and their controls as (mean±SD)

Parameter	CKD (stage5) (n= 33)	Control(n=34)	P value
NGAL (ng/ml)	486±153	296.4±83.5	<.0001***
hsCRP (µg/ml)	8.3±2.33	1.24±0.67	<.0001***
Cysttin-c (ng/ml)	10.3±5.7	5±1.45	<.0001***
eGFR (mL/min/1.73 m^2)	9.65±6.3	126.1±33.6	<.0001***
FSB (m. mol/l)	5.5±0.7	5.4±0.78	>0.05
Urea (m. mol/l)	54.6±24.1	10.3±1.7	<.0001***
Creatinine (µmol/l)	763.7±398	68±10.6	<.0001***

*p<0.05, ** p<0.01, *** p<0.0001, There are no significant differences in age (years) and BMI (kg/m2) between patients with end-stage renal disease and control group (43.3±14. 1 vs 38±11), (26.1±2. 3 vs 26.1±3.4) (p>0.05), while there are significant differences in other biochemical parameters except for glucose (table 2).

Table 3: Comparison between serum variables in renal transplanted patients (RT) and CKD patients (stage 5) (mean±SD)

Parameter	(RT)Patients(n= 35)	CKD (stage 5) (n= 33)	P value
NGAL (ng/ml)	455±145	486±153	<0.0001***
hs CRP (µg/ml)	5.9±3.2	8.3±2.33	<0.0001***
Cystatin-c (ng/ml)	7.1±1.9	10.3±5.7	<0.0001***
eGFR (mL/min/1.73 m^2)	82.3±31.1	9.65±6.3	<0.0001 ***
FBS (m. mol/l)	5.3±0.77	5.5±0.70	>0.05
Urea (m. mol/l)	22.1±10.7	54.6±24.1	<0.0001***
Creatinine (µmol/l)	135.9±57.9	763.7±398	<0.0001***

*p<0.05, ** p<0.01, *** p<0.001, There is a significant differences in age (years) and BMI (kg/m2) between patients with renal transplantation and CKD patients (stage5) (34±9.1 vs 43.4±14.1), but no significant differences in BMI between two groups (25.1±2.8 vs26.2±3.4) (p>0.05). There are significant differences in other biochemical parameters except glucose (table 3)

Table 4: Comparison between serum variables in renal transplantation patients (RT) according the transplantation duration as (mean±SD)

Parameters	After one month RT (n= 10)	After six month RT (n = 14)	P value
NGAL (ng/ml)	480±188	409±78	P<0.01**
hs CRP (µg/ml)	6.0±3.0	3.9±1.3	P<0.05*
Cystatin-c (ng/ml)	8±1.9	6.2±1.2	P<0.05*

*p<0.05, ** p<0.01, There are significant differences in serum NGAL and hsCRP between the RT patients after one, and six months of transplantation.

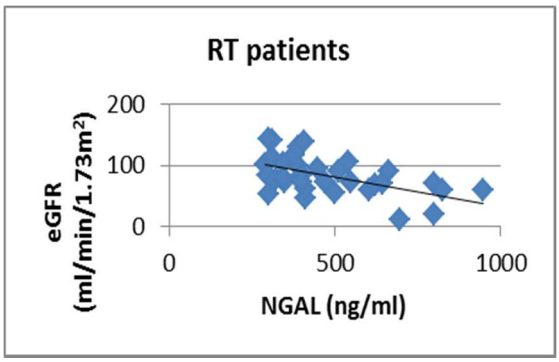

Fig. 1: Correlation between serum NGAL, and eGFR (r =-0.39, p<0.05) in RT patients

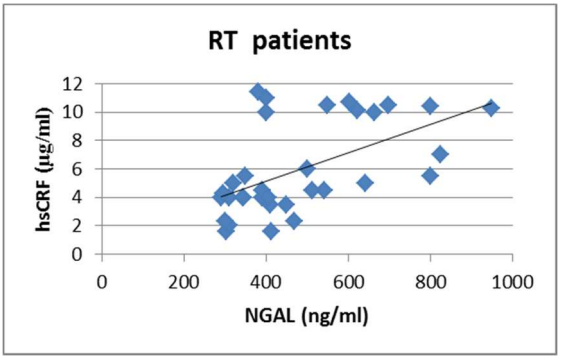

Fig. 2: Correlation between serum NGAL, and hsCRP (r = 0.43, p<0.01) in RT patients

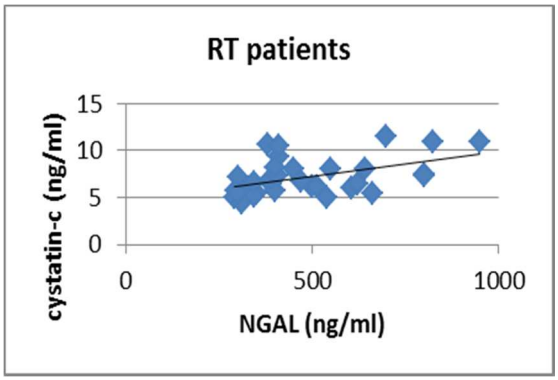

Fig. 3: Correlation between serum NGAL, and Cystatin-c (r = 0.39, p<0.05) in RT patients

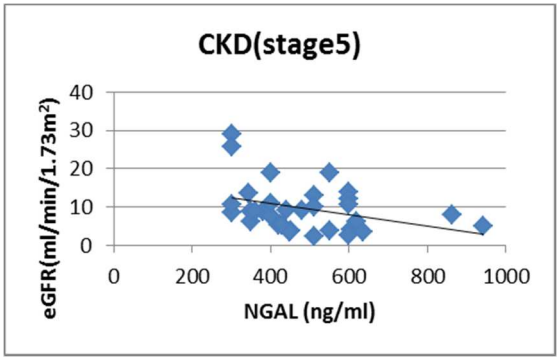

Fig. 4: Correlation between serum NGAL, and eGFR (r =-0.35, p<0.01) in CKD patients (stage 5)

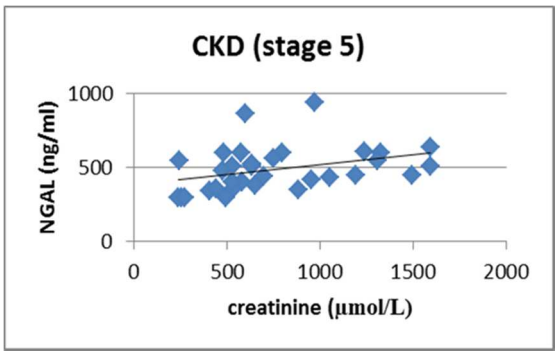

Fig. 5: Correlation between serum NGAL, and creatinine (r = 0.35, p<0.05) in CKD patients (stage5)

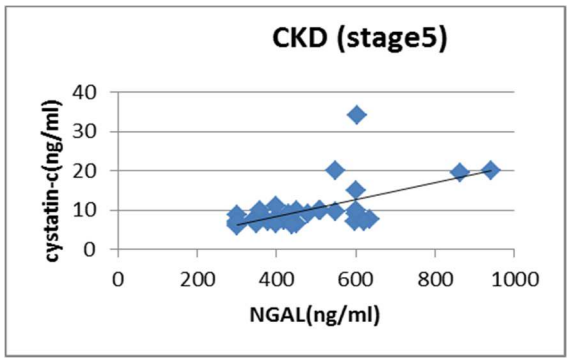

Fig. 6: Correlation between serum NGAL, and cystatin-c (r = 0.56, p<0.01) in CKD patients (stage5)

RESULTS AND DISCUSSION

An increase in serum creatinine concentration, which can be used for diagnosis of acute graft dysfunction, but it, is a late signal of kidney injury. Nevertheless, the sooner treatment is initiated, the better outcome is expected. In the present study, there was a significant increase in serum NGAL of renal transplantation patients, and CKD patients (stage-5) than in healthy control subjects included in this study as shown in table 1 and 2 respectively. A great interest on NGAL arose several years ago from several studies and was suggested as a new biomarker for the prediction of kidney injury and immediate post-transplant period because renal epithelia expresses and excrete NGAL in large quantities in urine following the kidney injury, and may be explained by more extensive renal damage [22-24]. Lebkowska U *et al.* in their study showed, on 41 patients on hemodialysis prior to kidney transplantation NGAL level significantly decreased in one day after successful kidney transplantation, before a falling in the main renal biomarkers such as serum cystatin-c or creatinine [25]. Another recent study concluded that serum NGAL level can be considered as a determining parameter for induction of emergency hemodialysis [26]. Previously creatinine was of one the most commonly used in laboratory parameter for CKD diagnosis in addition to others. However the creatinine level is affected by several factors such as gender and age, and it shows an elevation only after the 50 % loss of renal function so the creatinine value is considered a poor, indicative for AKI and it is unable to reflect acute renal injury as early as desired [27, 28]. A previous report considered NGAL as a marker for both acute kidney disease and the severity of CKD [29]. Acute tubular injury in AKI is believed to cause increased secretion of NGAL from neutrophils, macrophages, and other immune cells as an acute phase reactant [30]. Many other studies showed that serum NGAL level can be used as an important marker for initiation of renal replacement therapy (RRT) patients, or as an early sensitive marker of kidney impairment or injury [31-33]. Cross-sectional studies considered that CKD are also associated with increased concentrations of NGAL in both urine and plasma when compared to

normal individuals, although not to the same extent as in AKI [34, 35]. In this respect, Bolignano D *et al.* (2009) in their study showed that serum NGAL levels were higher in hemodialysis patients compared to the control subjects [36]. The present study showed a significant difference in serum NGAL between renal transplanted patients and CKD patients (stage-5) as shown in table 3. One recent study concluded that serum NGAL levels can be used for the evaluation of inflammation in CKD patients, including renal transplant patients together with other inflammatory biomarkers [37]. In addition, the present study was shown that serum NGAL is significantly higher in RT patients after one month of transplantation than in RT patients after six months, in addition to significant differences in both serum hsCRP, and serum cystatin-C between them as shown in table 4. Yarlagadda *et al.* in their study suggested that serum NGAL may be used as an early prediction of delayed graft function (DGF) in kidney transplantation [38]. DGF is associated with increased risk of graft loss and death, and usually, there is no effective treatment, so its early diagnosis and therapeutic intervention may improve outcome. Therefore the need for biomarkers of early diagnosis of acute kidney injury is great [39]. The NGAL is one of the important urinary and serum proteins that have been intensively investigated as a possible biomarker to diagnose DGF in kidney transplantation instead of creation, the poor biomarker for kidney injury due principally to its inability to help in the diagnosis of DGF [25]. In the present study the higher NGAL level, and the correlations between NGAL and other kidney parameters were studied (results and fig. 1-6) and are in agreement with many reports, which implies that NGAL is an early indicator biomarker for both RT and advanced CKD patients and can be used to start early treatment in these patients [39-42]. Malyszko et al. in their study showed that in patients with delayed graft function; there was no fall in serum NGAL or cystatin-c. Therefore, they concluded that NGAL should be investigated as early as possible, because it is a sensitive marker of kidney injury or impairment, which might provide an additional accurate measurement of kidney impairment in CKD and among transplant recipients, particularly at advanced stages [43]. Like other studies, Lebkowska etal study showed that, in renal transplantation, NGAL appears to be an early marker of acute rejection [25]. The plasma NGAL concentration was found to correlate well with measures of dialysis adequacy, suggesting its role for it in guiding the management of dialysis prescriptions in CKD subjects treated with chronic hemodialysis [39, 43, 44]. At last it is possible to say that serum NGAL should be used routinely in detecting and following up renal function impairment and in the detection of early rejection after kidney transplantation, and even for assessment of dialysis treatment.

CONCLUSION

Serum NGAL could be considered a sensitive biomarker of renal function and is emerging as a promising biomarker for the early detection and staging of CKD, for predicting progression, and for monitoring the response to interventions. Routine measurement of NGAL could increase the chances of early diagnosis of acute rejection, and improving the prognosis and quality of life of the transplanted patients. In addition, the investigation of NGAL is needed to be used as a potential early biomarker for DGF, especially in the starting the early dialysis treatment or anti-rejection therapy.

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CONFLICT OF INTERESTS

The authors declare that they have no competing of interests.

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