Serum Kallistatin as a Biomarker of Sepsis and Mortality in Geriatric Patients with Acute Kidney Injury

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SUMMARY

Kallistatin has beneficial effects on cardiorenal injury by inhibiting oxidative stress, angiogenesis and inflammation. However, the role in geriatric patients with acute kidney injury (AKI) has not been investigated in clinical studies. The aim of this study was to evaluate the relationship among kallistatin, cardiovascular biomarkers and mortality in geriatric patients with AKI and infection. In this observational, longitudinal study, 104 geriatric patients (age >65 years) with AKI were included. Serum kallistatin, NT-proBNP, troponin I and CK-MB were measured at first admission. Patients were evaluated according to the infection and/or sepsis status. The mean age of patients was 80±7.0 years. Twenty-five (24%) AKI patients died during hospitalization. The nonsurvivor geriatric patients with AKI were significantly older than survivors. Serum albumin and kallistatin levels were significantly lower, however, NT-proBNP and serum urea levels were significantly higher in nonsurvivors compared to survivors. Serum kallistatin levels in patients with sepsis were lower than in those without sepsis (10.2±3.9 *vs*. 17.4±2.5; p<0.001). The mortality rate was 4.6 higher in septic patients (46% *vs*. 10%; p<0.001). Serum kallistatin (Exp(B): 0.83 (0.73-0.94; p<0.01) and NT-proBNP (Exp(B): 1.001 (1.001-1.002); p<0.05) were independently associated with mortality. Serum kallistatin and NT-proBNP levels were associated with mortality of geriatric patients with AKI. In addition, the presence of sepsis in AKI may be responsible for low serum kallistatin levels. Large-scale studies are needed to clarify this issue.

KEYWORDS

Acute kidney injury; Geriatric patients; Elderly; Kallistatin; Brain natriuretic peptide; Cardiovascular biomarkers; Sepsis; Mortality

Introduction

Acute kidney injury (AKI) in geriatric population is common and increasing each year[1-3]. Hospitalization and mortality rates due to AKI have increased dramatically in the last 10 years[2]. Therefore, new studies focusing on biomarkers have been conducted to determine the diagnosis and mortality of AKI[3-6].

Kallistatin as a serine protease inhibitor has a vital role such as vasodilatation, anti-inflammation, antiangiogenesis and antioxidation[7-9]. These effects are a proven defense mechanism against cardiorenal injury and sepsis[7-12]. In addition, kallistatin levels decreased in animal studies with sepsis, and replacement therapy may protect the kidney and improve mortality rates[13,14]. Nonetheless, clinical research about the role of serum kallistatin in AKI mortality is yet to be performed.

Natriuretic peptides and other cardiac enzymes have been widely used in the diagnosis and prognosis of the acute coronary syndrome and cardiorenal syndrome[15]. These parameters are also known to increase in some kidney diseases and may be associated with cardiovascular injury in chronic kidney disease (CKD)[15,16]. However, the association of cardiovascular biomarkers with mortality has not been adequately investigated, especially in geriatric patients with AKI. The aim of this study was to investigate the relationship among serum kallistatin, cardiovascular biomarkers and mortality in geriatric patients with AKI and infection.

Materials and Methods

During a two-year period, patients aged over 65 years admitted to our hospital for AKI were included in the study. Patients with postrenal AKI, under 65 years of age, chronic renal replacement therapy (RRT), end-stage cancer and liver diseases were excluded.

The AKI was defined as an increase in serum creatinine (SCr) by 50% within 7 days or increase in SCr by 0.3 mg/dL (26.5 mmol/L) or more within 2 days or urine volume ≤0.5 mL/kg/h for at least 6 hours according to the Kidney Disease Improving Global Outcomes (KDIGO) 2012 criteria[17]. Indications for acute dialysis were serum potassium ≥6.0 mmol/L or serum urea >300 mg/dL or serum bicarbonate <10 mmol/L despite medical treatment, acute pulmonary edema, acute uremic encephalopathy, or pericarditis. Sepsis is now defined as a life-threatening organ failure caused by the host's inappropriate response to infection. Clinical criteria include suspected or documented infection and acute changes of two or more Sequential Organ Failure Assessment scores[18].

Patient data were recorded during hospital stay. Demographic characteristics and medical history (systemic diseases, drugs, blood pressure levels, and laboratory results) were obtained from hospital records. Decision on RRT was defined according to clinical and laboratory results. Serum kallistatin, N-terminal pro-B-type natriuretic peptide (NT-proBNP), troponin I and creatine kinase-myocardial band (CK-MB) were measured at first admission. Neutrophil/lymphocyte ratio (NLR) was defined by the ratio of neutrophil count to lymphocyte count. Patients were grouped according to the median level of serum kallistatin, i.e., <12.2 ng/mL as group 1 and ≥12.2 ng /mL as group 2. NT-proBNP levels were divided according to the median level.

Human kallistatin levels were determined with a commercially available ELISA kit (Sunred Biological Technology Co., Ltd., Shanghai, China) with the principle of double-antibody sandwich technique, according to the manufacturer's instructions. NT-proBNP levels were measured with an immunoassay technology and time resolved

fluorometric detection in AQT90 FLEX analyzer with the test kit of the manufacturer (Radiometer Medical ApS, Bronshoj, Denmark). Troponin I and CK-MB levels were determined in a DXI-800 analyzer with chemiluminescent method (Beckman Coulter Diagnostic Division Headquarters, Brea, CA, USA).

Ethical approval

In study patients, all the procedures were implemented after approval of the Izmir Bozyaka Training and Research Hospital Ethics Committee. This study was carried out in accordance with the Helsinki Declaration standards. Informed consent was obtained from all individual participants included in the study.

Statistical analysis

Statistical analyses were performed by SPSS 15.0 for Windows package program. Mean value with standard deviation (mean ± SD) and median [interquartile range] were calculated for all parameters. Pearson correlation test was used for relations of parameters with homogeneous distribution and Spearman rho test was used for non-homogeneously distributed parameters. Student's t-test and χ^2-test were used for comparison between two groups. Cox regression analysis was used to detect independent predictors of both mortality and sepsis. The mortality rates between the groups were compared by Kaplan-Meier analysis. The level of statistical significance was set at $p<0.05$.

Results

There were 104 patients, mean age 80±7.0 (65-95), 45 (43.2%) of them male. Demographic and laboratory values are shown in Table 1. The mean follow up time was 11±7.0 (2-31) days. Mortality rate during hospital stay was 24% (n=25). When compared with surviving patients, the mean age, serum urea, C-reactive protein (CRP), NT-proBNP, percentage of infection and sepsis were significantly higher; however, serum kallistatin ($p<0.05$) and albumin levels were significantly lower in nonsurviving patients (Table 1).

In Cox regression analysis (age, presence of sepsis, serum urea, serum albumin, NT-proBNP, CRP, and serum kallistatin level), serum kallistatin level (Exp(B): 0.83 (CI:0.73-0.94); $p<0.01$) and serum NT-proBNP (Exp(B):1.001(CI:1.001-1.002); $p<0.05$) were independently associated with mortality.

Acute infection and sepsis

Fifty-three percent (n=55) of patients had infection including lower respiratory tract infection (60%), urinary tract infection (36.3%), soft tissue infection (2.5%) and others (1.2%) at first admission. When compared to patients without infection, total leukocyte count (15.4±8.5 *vs*. 9.5±3.6; $p<0.001$), NLR (12.2±9.8% *vs*. 8.4±7.5%; $p=0.02$), and CRP level (139±96 *vs*. 84±88; $p<0.01$) were higher and serum albumin level (2.8±0.5 vs 3.1±0.6; $p=0.02$) lower in the presence of infection. Mortality rates were significantly higher (33% *vs*. 14%; $p=0.02$) in patients with infection. However, serum kallistatin levels were relatively lower in patients with infection (14.0±11.1 ng/mL, 15.1±10.0 ng/mL; $p=0.6$).

Sepsis developed in 41 (39.4%) patients. Acute phase reactants and mortality were significantly higher, and serum kallistatin levels (10.2±3.9 ng/

TABLE 1. Demographic and laboratory results of all study patients and comparison of surviving and nonsurviving patients

	All patients (n=104), mean ± SD	Nonsurvivors (n=25), mean ± SD	Survivors (n=79), mean ± SD	p value
Age (years)	80±7.0	83±7.3	79±6.8	0.04*
Sex (male/female) (%)	43.2	60	56	0.7
Presence of infection (%)	53	72	47	0.02*
Sepsis (%)	39.4	76	28	<0.001*
Diabetes mellitus (%)	34	36	33	0.8
Cardiovascular disease (%)	49	60	45	0.2
Acute dialysis (%)	29.8	40	27	0.2
Laboratory results				
Glucose (mg/dL)	151±76	153±77	150±76	0.8
Serum urea (mg/dL)	168±77	205±92	156±68	<0.01*
Serum creatinine (mg/dL)	3.8±2.3	3.6±1.9	3.8±2.4	0.5
Serum bicarbonate (mmol/L)	18±5.2	18.5±4.9	18.3±5.2	0.8
Serum lactate (mmol/L)	2.2±1.5	2.5±1.1	2.0±1.7	0.2
Albumin (g/dL)	3.2±0.5	2.9±0.6	3.3±0.5	0.02*
C-reactive protein (mg/L)	114±96	168±94	97±91	0.01*
Hemoglobin (g/dL)	11±2.1	11±2.3	10.6±2.0	0.4
Total leukocyte count (mm^3/1000)	12.6±7.3	14.0±7.4	12.2±7.0	0.3
NLR (%)	10.4±8.9	11.9±6.9	10.0±9.5	0.3
Serum kallistatin (ng/mL) [median (IQR)]	14.5±10.5 [12.2 (6.7)]	7.47±3.7 [9.3 (7.3)]	14.6±9.1 [13.0 (6.0)]	0.01*
NT-proBNP (pg/mL) [median (IQR)]	813±975 [442 (799)]	1276±1362 [726 (1823)]	663±767 [406 (489)]	0.04*
Troponin (ng/ mL) [median (IQR)]	0.74±2.68 [0.06 (0.33)]	0.37±0.73 [0.09 (0.50)]	0.85±3.0 [0.04 (0.28)]	0.4
CK-MB (ng/mL) [median (IQR)]	10.3±33 [3.70 (5.0)]	6.40±14 [3.70 (3.0)]	11.6±37 [3.75 (6.0)]	0.5

SD = standard deviation; NLR = neuthrophil-lymphocyte ratio, NT-proBNP = N-terminal pro-B-type natriuretic peptide; CK-MB = creatine kinase-myocardial band; p<0.05 was considered statistically significant

TABLE 2. Comparison of patients with and without sepsis

	With sepsis (n=41), mean ± SD	Without sepsis (n=63), mean ± SD	p value
Age (years)	82.3±6.9	78.7±6.7	0.01*
Sex (male/female) (%)	56	57	0.9
Diabetes mellitus (%)	35	34	0.9
Cardiovascular disease (%)	49	49	0.9
Emergency renal replacement therapy (%)	27	32	0.5
Mortality (%)	46	10	<0.001*
Laboratory results			
Glucose (mg/dL)	154±81	149±73	0.7
Serum urea level (mg/dL)	152±62	178±84	0.08
Serum creatinine level (mg/dL)	3.1±1.4	4.2±2.6	0.01*
Serum bicarbonate (mmol/L)	18±4.7	19±5.7	0.2
Serum lactate (mmol/L)	2.4±1.4	2.0±1.6	0.1
Albumin (g/dL)	2.7±0.5	3.2±0.5	<0.001*
C-reactive protein (mg/L)	169±97	76±77	<0.001*
Hemoglobin (g/dL)	10.5±2.1	10.8±2.1	0.5
Total leukocyte count (mm^3/1000)	15.5±9.4	10.7±4.5	<0.01*
NLR (%)	13.4±10.3	8.5±7.3	0.01*
Serum kallistatin (ng/mL) [median (IQR)]	10.2±3.9 [10.9 (5.43)]	17.4±2.5 [14.0 (8.33)]	<0.001*
NT-proBNP (pg/mL) [median (IQR)]	972±1125 [546 (1021)]	706±855 [396(495)]	0.2
Troponin (ng/mL) [median (IQR)]	0.96±3.3 [0.09 (0.42)]	0.58±2.1 [0.03 (0.21)]	0.4
CK-MB (ng/mL) [median (IQR)]	10.5±20 [3.70 (6.0)]	10.2±39 [3.75 (3.0)]	0.9

SD = standard deviation; NLR = neuthrophil-lymphocyte ratio; NT-proBNP = N-terminal prohormone of brain natriuretic peptide, CK-MB = creatine kinase-myocardial band; p<0.05 was considered statistically significant

mL, 17.4±12.5 ng/mL; p<0.001) were lower in septic patients. However, significant relationship between sepsis and cardiovascular biomarkers was not demonstrated. Comparison of patients with and without sepsis is illustrated in Table 2. Serum kallistatin (Exp(B): 0.86 (CI:0.76-0.97; p=0.01) and serum CRP levels (Exp(B):1.008 (CI:1.002-1.0014; p<0.01) were associated with sepsis on Cox regression analysis (variables: total leukocyte count, serum albumin, CRP, and serum kallistatin level).

Serum kallistatin and cardiovascular biomarkers (NT-proBNP, troponin and CK-MB)

The mean level of serum kallistatin was 14.5±10.5 ng/mL (1.8-64.2). When patients were grouped according to the median level of serum kallistatin <12.2 ng/mL as group 1 and ≥12.2 ng/mL as group 2, serum albumin (2.8±0.6 *vs*. 3.3±0.5; p=0.02) was lower and CRP level (139±109 *vs*. 94±85; p=0.04) higher in group 1. Serum kallistatin levels were significantly correlated with serum albumin (rho:0.32, p=0.003) and CRP (rho:-0.23, p=0.03). Correlation analysis is shown in Figure 1. Moreover, acute infection, sepsis and mortality rates were significantly higher (68% *vs*. 43%; p=0.01, 57% *vs*. 25%; p<0.01, and 32% *vs*. 14%; p=0.04, respectively) than in group 2. On the Kaplan Meier analysis, the mortality rates were higher in group 1 (log rank (Mantel-Cox) χ^2: 7.33; p<0.01). These data are shown in Figure 2. However, significant relationship between serum kallistatin and cardiovascular biomarkers was not recorded.

The mean NT-proBNP level was 813±975 ng/mL (35-4942). Serum NT-proBNP levels were correlated with troponin (rho: 0.43, p<0.001), CK-MB (rho:0.22, p=0.02) and hemoglobin (rho:-0.23; p=0.03). When patients were divided according to the median value of NT-proBNP (<465 ng/mL *vs*. ≥465 ng/mL), hemoglobin (10.2±2.2 *vs*. 11.2±1.9; p=0.01) was lower, whereas cardiovascular disease (60% *vs*. 38%; p=0.03) and mortality rates (31% *vs*. 17%; p=0.04) were significantly higher in the high NT-proBNP group. However, the

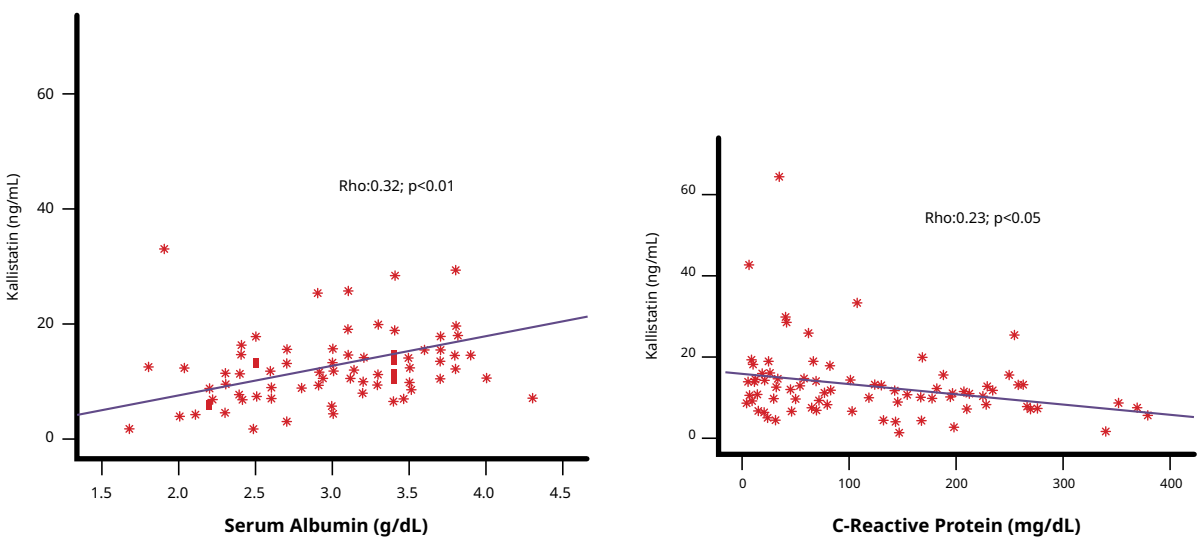

FIG. 1. Correlations of serum kallistatin levels with serum albumin (g/dL) and C-reactive protein (mg/dL).

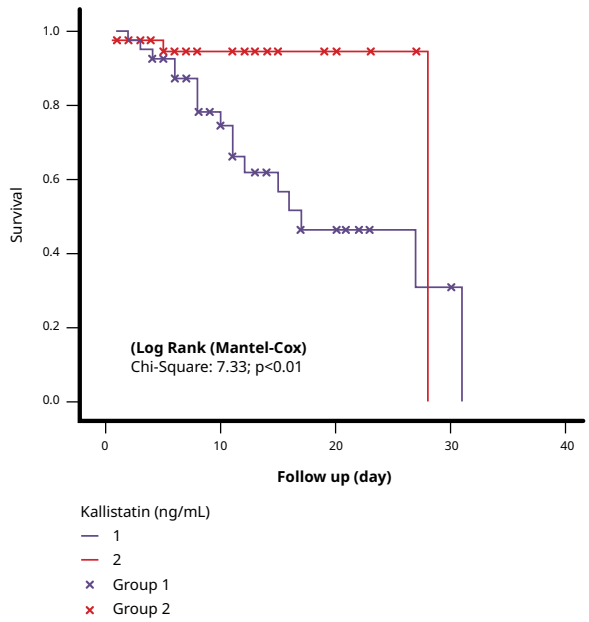

FIG. 2. Survival rates according to high (group 1) and low (group 2) serum kallistatin on Kaplan-Meier analysis.

relationship between NT-proBNP levels and other parameters (such as serum kallistatin) was not significant.

Discussion

We found a relationship between serum kallistatin and mortality in geriatric patients with AKI. A significant decrease in serum kallistatin level was also determined in septic patients with AKI.

Kallistatin exerts its beneficial effects by regulating inflammation, angiogenesis, apoptosis, oxidative stress, and fibrosis[7-9]. Recent studies have reported kallistatin as a target molecule for inflammatory diseases such as cancer, diabetes, cardiovascular diseases, cirrhosis, and sepsis[10-12,19,20]. Experimental studies also showed therapeutic role of kallistatin, especially in sepsis[21,22]. A significant decrease of kallistatin levels has been reported in septic animal studies, and its replacement demonstrated a moderating role in oxidative regulation[13,14]. Kallistatin protects organ damage by increasing nitric oxide (NO) and endothelial NO synthase levels. Lin *et al*. found that serum kallistatin levels decreased in 86 septic patients in the intensive care unit[19]. At the same time, serum kallistatin levels decreased in septic shock according to the severity of sepsis, and it was found to be related to mortality[19]. Kim *et al*. report that serum kallistatin was independently associated with mortality in septic shock[20]. Moreover, Vilander *et al*. showed that SERPINA4 gene encoding kallistatin was associated with KDIGO stage 2-3 AKI in critically ill patients[23]. In our study, we found a significant decrease in serum kallistatin levels in septic patients and determined an independent relationship between serum kallistatin levels and sepsis. Infections and sepsis are the major causes of AKI in geriatric patients[3,21,24]. In our study, the rates of infection and sepsis were 53% and 40% of cases. These results suggest the role of kallistatin as a biomarker in predicting mortality in sepsis with AKI.

Kallistatin has a substantial role in the renal system[7-9]. Reduction of serum kallistatin levels by administration of anti-kallistatin antibodies in rat models led to oxidative stress, inflammation and NO reduction in the kidneys[8]. This reduction caused both histopathologic changes (such as glomerulosclerosis, interstitial inflammation, and tubular atrophy) in the kidney and deterioration of kidney function parameters[7,9,13]. Kallistatin replacement therapy in renal ischemia-reperfusion experimental models has been shown to improve renal injury[24]. Our study established a decrease in serum kallistatin among the nonsurviving patients with AKI independently of septicemia. This suggests that kallistatin plays an important role in kidney injury.

Brain natriuretic peptide (BNP) is synthesized by cardiomyocytes in response to cardiovascular

injury[15]. BNP levels increase in the process of CKD[16,25]. This increase is well determined as a cardiovascular and overall mortality biomarker for all CKD stages[15,16,25]. However, there are not enough studies in the literature regarding the importance of BNP in AKI. De Cal *et al.*[26] demonstrated that BNP increased by an average of 4- to 10-fold in patients with AKI in the intensive care unit. Chou *et al.*[27] observed a variation in BNP within 48 hours as a considerable parameter for the prediction of renal outcome and mortality. In our study, BNP was increased in nonsurviving patients and it was associated with mortality. This increment may be an indicator of cardiovascular injury associated with hypervolemia in patients with AKI.

This study had some limitations. Firstly, it included a relatively low number of cases and no control group. However, this study was a clinically first, pioneering work in the literature. Secondly, this study just included mortality in the hospital, whereas the surviving patients were not evaluated after discharge.

Conclusion

Serum levels of NT-proBNP and kallistatin were associated with mortality of the geriatric patients with AKI. Serum kallistatin is a prominent biomarker in AKI. Sepsis may be responsible for the low levels of serum kallistatin. However, further large-scale controlled studies are needed for clinical usage of these biomarkers. ■

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SAŽETAK

Kalistatin u serumu kao biomarker za sepsu i smrtnost kod gerijatrijskih bolesnika s akutnim oštećenjem bubrega

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Kalistatin ima povoljan učinak na srčano i bubrežno oštećenje tako što suzbija oksidativni stres, angiogenezu i upalu. Međutim, njegova uloga kod gerijatrijskih bolesnika s akutnim oštećenjem bubrega (AOB) nije ispitana u kliničkim istraživanjima. Cilj ovog istraživanja bio je procijeniti odnos kalistatina, srčanožilnih biomarkera i smrtnosti u gerijatrijskih bolesnika s AOB i infekcijom. Ova opservacijska longitudinalna studija uključila je 104 gerijatrijska bolesnika (dob >65 godina) s AOB. Kalistatin, NT-proBNP, troponin I i CK-MB mjereni su kod njihovog prvog prijma u bolnicu. Bolesnici su procijenjeni prema stanju infekcije i/ili sepse. Srednja dob bolesnika bila je 80±7,0 godina. Tijekom boravka u bolnici umrlo je 25 (24%) bolesnika s AOB. Gerijatrijski bolesnici s AOB koji su umrli bili su značajno stariji od onih koji su preživjeli. Razine albumina i kalistatina u serumu bile su značajno niže, a razine NT-proBNP i ureje značajno više u bolesnika koji nisu preživjeli u usporedbi s onima koji su preživjeli. Razine kalistatina u serumu kod bolesnika sa sepsom bile su niže nego u onih bez sepse (10,2±3,9 prema 17,4±2,5; p<0,001). Stopa smrtnosti bila je 4,6 puta viša u bolesnika sa sepsom (46% prema 10%; p<0,001). Kalistatin (Exp(B): 0,83 (0,73-0,94); p<0,01) i NT-proBNP (Exp(B): 1,001 (1,001-1,002); p<0,05) u serumu bili su neovisno udruženi sa smrtnošću. Razine kalistatina i NT-proBNP u serumu bile su udružene sa smrtnošću gerijatrijskih bolesnika s AOB. Usto, prisutnost sepse kod AOB mogla bi biti odgovorna za niske razine kalistatina u serumu. Veće studije su potrebne kako bi se razjasnilo ovo pitanje.

KLJUČNE RIJEČI

Akutno oštećenje bubrega; Gerijatrijski bolesnici; Starije osobe; Kalistatin; Moždani natriuretski peptid; Srčanožilni biomarkeri; Sepsa; Smrtnost