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CLINICAL STUDY

Can serum NGAL levels be used as an inflammation marker on hemodialysis patients with permanent catheter?

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Abstract

Background: Neutrophil gelatinase-associated lipocalin (NGAL) is a member of lipocalin family and released from many tissues and cells. We aimed to investigate the relationship among serum NGAL levels, the inflammation markers (IL-6, hs-CRP, TNF-α) and different vascular access types used in dialysis patients. *Methods*: The study population included 90 patients and 30 healthy age-matched controls. The patients were divided into three groups (I, II, III) and group IV included the controls. In group I and II, the patients were with central venous permanent catheter and arterio-venous fistula, respectively. Group III included 30 patients with chronic renal failure. Hemogram, biochemical assays, ferritin, IL-6, hs-CRP, TNF-α, and NGAL were evaluated in all groups. *Results*: Serum NGAL levels were markedly higher in group I than in group II (7645.80 ± 924.61 vs. 4131.20 ± 609.87 pg/mL; $p < 0.05$). Positive correlation was detected between NGAL levels and duration of catheter (*r*: 0.903, *p*: 0.000), hs-CRP (*r*: 0.796, *p*: 0.000), IL-6 (*r*: 0.687, *p*: 0.000), TNF-α (*r*: 0.568, *p*: 0.000) levels and ferritin (*r*: 0.318, *p*: 0.001), whereas NGAL levels were negatively correlated with serum albumin levels (*r*: −0.494, *p*: 0.000). In multiple regression analysis, duration of catheter hs-CRP and TNF-α were predictors of NGAL in hemodialysis patients. *Conclusion*: Inflammation was observed in hemodialysis patients and increases with catheter. Our findings show that a strong relationship among serum NGAL levels, duration of catheter, hs-CRP and TNF-α. NGAL may be used as a new inflammation marker in hemodialysis patients.

Keywords

Central venous permanent catheter, hemodialysis, interleukin-6, neutrophil gelatinase-associated lipocalin, tumor necrosis factor-alpha

History

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Introduction

The first necessity of an efficient hemodialysis (HD) is to obtain an eligible vascular access that is capable of sustaining an efficient blood flow. Vascular access (VA) is the ''Achilles tendon'' for HD patients. Arteriovenous fistula (AVF) is preferred to arteriovenous graft (AVG) and central venous permanent catheter (CVPC), due to its long-term patency and lower complication rates. In recent years, usage of CVPC for VA has been increasing due to various reasons, such as older age, delayed referral to the nephrologist, obesity, presence of diabetes mellitus and peripheral vascular diseases.[1]

Inflammation is a common condition in patients with chronic renal failure (CRF), especially in hemodialyzed patients. Uremia can cause an inflammatory process by stimulating proinflammatory cytokines due to exposure of the blood to the dialysate and dialysis membrane during extracorporeal circulation. An increase in the oxidative metabolism of circulating neutrophiles is apparent in these patients. It has been reported that during dialysis, dialyzers most likely activate a complement system via an alternative path and bind IgG and complementary elements to the dialysis membrane. This creates a bioactive surface for granulocytes and stimulates degranulation and the activation of neutrophiles that make contact with it.[2–4]

Neutrophil gelatinase-associated lipocalin (NGAL) is a protein member of the lipocalin family with a weight of 25 kDa and contains 178 amino acids. NGAL is thought to have correlation with other inflammatory markers in various inflammatory conditions. It is stored in specific granules in neutrophiles and up-regulated as a response to a variety of conditions like inflammation, ischemia, infections, neoplasia, and atherosclerosis.[5–7] Nephrologists have recently discovered that NGAL is released from damaged renal tubular cells, and it is hoped that this will be a possible marker for acute and chronic renal diseases. Also, NGAL is a small molecule that can be freely filtrated through glomerulus and reabsorbed from proximal tubules with megalin-dependent endocytosis at high rates. In CRF, increased serum NGAL level depends on decreased glomerular filtration rate and therefore accumulation in the blood by decreased NGAL clearance. Increased NGAL level in urine and blood is an indicator of acute kidney failure and provides opportunity to the clinicians for applying timely and efficient treatment.[8]

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NGAL level is reported to be in a strong correlation with renal injury level in chronic diseases, such as diabetic nephropathy, autosomal polycystic renal disease, and proteinuric glomerulonephritis.[9–11] In addition, Malyszko et al.[12] showed that NGAL was related with the markers of inflammation in HD patients.

The purpose of this study is to assess the relationship among serum NGAL levels, VA type and inflammation markers in HD patients without active infection and/or inflammation.

Materials and methods

Study protocol

The study population includes 90 patients and 30 healthy age and sex-matched controls. Patients were divided into three groups. Group I patients ($n = 30$) were on routine HD with CVPC and group II patients ($n = 30$) were on routine HD with AVF. Group III includes 30 patients with CRF (stage 3–4) but not on routine HD and group IV includes the control subjects. The study was approved by the Local Ethic Committee and all patients gave written informed consent. All subjects underwent detailed clinical examination. Demographic information and medical history of patients were obtained at baseline by interview with patients and review of the medical records.

Groups I and II patients have received regular HD treatment three times in a week for 4 h and all of them were anuric. HD was performed using bicarbonate-contained dialysate and synthetic polysulfone dialyzer membranes. HD patients who had stable dry-weight with no volume overload for at least 2 months were enrolled to the study. Patients who had been receiving HD for less than 3 months, who had CVPV for less than 3 months, who had hematocrit levels below 33%, hemoglobin levels below 11 g/dL, bleeding diathesis, infection, malignant diseases, active vasculitis, active liver diseases, severe hyperparathyroidism, and who were receiving intravenous iron administration, erythropoietin, anti-inflammatory, and antioxidant treatment at the last month were excluded from the study.

About 8–10 cc venous blood samples from the antecubital vein were taken from each patient of the four groups between 8.00 and 9.00 a.m. after at least 8–12 h of fasting (just before dialysis with the HD patients). Complete blood counts, biochemical parameters, and ferritin were studied within the same day of sampling. The blood was centrifuged for 5 min at 3500 rpm after waiting half an hour for hs-CRP, IL-6, TNF-α, and NGAL analyses of blood that have been taken. Serum was separated and stored in a deep-freeze at −20 °C for later analysis.

Kt/V_{urea} calculations of the patients were made on-line via the Hypertension Dialysis and Clinical Nephrology website (www.hdcn.com) by submitting patients' dialysis technique and test results.

The glomerular filtration rate (GFR) of pre-dialysis patients was calculated using the Cockcroft-Gault formula, although it has relatively low sensitivity:

$$\mathrm{GFR} = \frac{(140 - \mathrm{age}) \times \mathrm{weight(kg)}}{\left\{ \begin{array}{c} 72 \times \text{serum creatinine} \\ (\text{the results were multiplied by } 0.85 \\ \text{for female patients}) \end{array} \right\}}$$

The body mass indexes (BMI) of all the patients and the healthy controls were calculated by the formula: [Body weight (kg)/height^2].

For blood samples, complete blood count was studied with the Siemens Advia 2120i Hematology system (Siemens Healthcare Diagnostic ING., Tarrytown, NY), biochemical parameters with Olympus AU 2700 autoanalyzer (Olympus Corporation, Tokyo, Japan) using specific kits for machines. Ferritin level was designated with Siemens branded eligible kits (Siemens Healthcare Diagnostics ING, USA). TNF-α (Catalog No: TR75111) was examined using the ELISA method (Tani Medical, Turkey; Sensitivity 0.5–5.5 pg/mL). IL-6 (Catalog No: EK0410) and NGAL (Catalog No: EK0853) were examined using the ELISA method (Boster Biological Technology Co, Ltd, USA; IL-6 sensitivity <0.3 pg/mL, NGAL sensitivity <10 pg/mL). hs-CRP (Catalog No: KAPDB4360) was examined using the nephelometric method (DIAsource ImmunoAssays SA, Belgium; hs-CRP sensitivity 10 ng/mL).

Statistical analysis

The statistical analysis was performed using the SPSS 15.00 computer statistic program (SPSS Inc., Software, Chicago, IL). Numeric data are presented as mean ± standard deviation; categorical data are presented as number and percentage. Comparisons among groups were performed using the one-way ANOVA test, Student's *t*-test for unpaired, normally distributed data and Chi-square test for categorical data. The Pearson correlation analysis was performed to test correlations between NGAL and other variables considered in the study. Multiple regression analysis was used to determine independent factors affecting the dependent variable (NGAL). Data were expressed as partial correlation coefficients (β) and *p* value. *p* Values less than 0.05 were considered as statistically significant.

Results

The demographic features and laboratory parameters of the study groups are summarized in Table 1. The mean age of the 90 patients (46 men and 44 women) was 50.98 ± 11.22 (range 24–69) years. The mean duration of HD in all HD patients was 30.63 ± 16.89 (range 5–76) months and the mean duration of CVPC usage was 10.33 ± 4.48 (range 3–19) months. Underlying renal diseases in all patients were DM in 35 (38.9%) patients, hypertension in 30 (33.3%) patients, chronic glomerulonephritis in 9 (10%) patients, nephrolithiasis in 6 (6.67%) patients, chronic pyelonephritis in 6 (6.67%) patients, polycystic kidney disease in 2 (2.22%) patients, and unknown in 2 (2.22%) patients. There was no significant difference in terms of age, gender, BMI, duration of HD, white blood cells (WBC) and Kt/V_{urea} among patients groups ($p > 0.05$).

Serum mean NGAL levels were significantly higher in all patient groups than in healthy subjects ($p < 0.05$). Especially, HD patients with CVPC had the highest serum NGAL levels (7645.80 ± 924.61 pg/mL). Significant difference in serum NGAL levels was observed between patients with CVPC and AVF (7645.80 ± 924.61 pg/mL vs. 4131.20 ± 609.87 pg/mL, $p < 0.05$) and between patients with AVF and stage 3–4 CRF

Table 1. Demographic features and laboratory parameters of study groups*.

	Group I (CVPC) $n=30$	Group II (AVF) $n=30$	Group III (Stage 3–4 CRF) $n=30$	Group IV (Control group) $n=30$	P
Age (year)	53.10 ± 10.23	51.40 ± 13.11	48.46 ± 9.93	50.26 ± 9.82	NS
Gender (F/M)	16/14	14/16	14/16	13/17	NS
Duration of HD (months)	28.06 ± 15.33	33.20 ± 18.21	–	–	NS
GFR (ml/)	§	§	34.27 ± 10.13	¶	
Duration of CVPC (months)	10.33 ± 4.48	–	–	–	
Kt/Vurea	1.33 ± 0.08	1.36 ± 0.06	–	–	NS
BMI (kg/m^2)	22.34 ± 2.85	22.44 ± 2.45	23.59 ± 2.21	23.40 ± 3.26	NS
Albumin (g/dl)	3.53 ± 0.35	4.02 ± 0.34	4.13 ± 0.27	4.61 ± 0.28	a,b,c,e,f
Haemoglobin (g/dl)	11.30 ± 0.84	11.58 ± 0.82	12.51 ± 1.11	13.46 ± 0.64	b,c,d,e,f
White blood cells (mm^3)	6741.33 ± 1872.15	6324.00 ± 1560.72	7042.66 ± 1452.08	6019.00 ± 1215.73	NS
Ferritin (ng/ml)	277.00 ± 73.65	233.93 ± 68.66	197.16 ± 40.92	100.96 ± 23.47	a,b,c,e,f
hs-CRP (ng/ml)	7115.76 ± 782.12	4239.10 ± 888.36	3464.53 ± 717.41	1730.70 ± 627.07	a,b,c,e,f
IL-6 (pg/ml)	4.85 ± 0.59	3.50 ± 0.48	3.03 ± 0.80	1.61 ± 0.24	a,b,c,d,e,f
TNF-α (pg/ml)	17.70 ± 1.20	15.57 ± 2.17	12.37 ± 3.97	1.56 ± 0.65	a,b,c,d,e,f
NGAL (pg/ml)	7645.80 ± 924.61	4131.20 ± 609.871	3685.60 ± 481.08	1308,66 ± 371.12	a,b,c,d,e,f

Notes: *Data given means ± SD and n (%).
GFR: glomerular filtration rate; BMI: body mass index; hs-CRP: high sensitive-C reactive protein; TNF-α: tumor necrosis factor-alpha; IL-6: interleukin-6; NGAL: neutrophil gelatinase-associated lipocalin.
§: Anuric; ¶: Not calculated.
NS: non-significant; $p>0.05$.
[a]Comparison between group I and group II is $p<0.05$.
[b]Comparison between group I and group III is $p<0.05$.
[c]Comparison between group I and group IV is $p<0.05$.
[d]Comparison between group II and group III is $p<0.05$.
[e]Comparison between group II and group IV is $p<0.05$.
[f]Comparison between group III and group IV is $p<0.05$.

(4131.20 ± 3685.60 pg/mL vs. 3685.60 ± 481.08 pg/mL, $p<0.05$) and between patients with CVPC and stage 3–4 CRF (7645.80 ± 924.61 pg/mL vs. 3685.60 ± 481.08 pg/mL, $p<0.05$).

We noted that serum hs-CRP, TNF-α, IL-6, and ferritin levels were the highest in HD patients with CVPC and the lowest in stage 3–4 CRF patients ($p<0.05$). Serum hs-CRP, TNF-α, IL-6, and ferritin levels were significantly higher in all patient groups than in healthy controls ($p<0.05$). There were significant differences between patients with CVPC and AVF with regard to serum hs-CRP, TNF-α, IL-6, and ferritin levels ($p<0.05$).

Although serum albumin levels were within the normal range in all groups (3.5–5.3 g/dL), mean serum albumin level was significantly low in group I patients with CVPC (3.53 ± 0.35 g/dL; $p<0.05$) among all patient groups.

There was a significant difference among patient groups in terms of mean serum IL-6 levels. Serum IL-6 levels were significantly higher in all patient groups than in healthy controls ($p<0.05$).

In Pearson's correlation analysis, NGAL was directly correlated with duration of CVPC (r: 0.903, p: 0.000), hs-CRP (r: 0.796, p: 0.000), IL-6 (r: 0.687, p: 0.000), TNF-α (r: 0.568, p: 0.000), and ferritin levels (r: 0.318, p: 0.001), whereas a significant inverse correlation was detected with albumin levels (r: −0.494, p: 0.000) in HD patients. In contrast, no significant correlation was found among serum NGAL levels and age (r: 0.083, p: 0.524), WBC levels (r: 0.092, p: 0.483), duration of HD (r: −0.176, p: 0.287) and Kt/V_{urea} (r: −0.143, p: 0.246). The correlation of serum NGAL levels with variables in all patient groups are showed in Table 2**.** All variables that were found to be significantly related to NGAL levels in univariate analysis were introduced in a multivariate model using NGAL as a dependent variable. After adjustment for other factors, significance was maintained for correlation among NGAL and duration of CVPC usage (β: 0.64, p: 0.00) (Figure 1), hs-CRP (β: 0.30, p: 0.00) (Figure 2) and TNF-α levels (β: 0.12, p: 0.02) (Figure 3).

Table 2. Correlation of serum NGAL levels with variables in all patients groups.

	Group I (CVPC)		Group II (AVF)		GroupIII (Stage3-4 CRF)	
	r	p	r	p	r	p
Age	0.174	0.359	0.104	0.585	0.216	0.252
BMI	−0.226	0.231	0.235	0.211	0.177	0.349
WBC	−0.117	0.539	0.082	0.672	0.123	0.518
Kt/V_{urea}	0.272	0.147	0.043	0.823	NA	NA
Duration of HD	0.204	0.279	0.089	0.640	NA	NA
hs-CRP	0.470	0.002*	0.412	0.005*	0.457	0.011*
TNF-α	0.394	0.009*	0.417	0.002*	0.356	0.023*
IL-6	0.439	0.015*	0.522	0.008*	0.518	0.003*
Albumin	−0.527	0.008*	−0.418	0.002*	−0.336	0.001*
Duration of CVPC	0.739	0.000*	NA	NA	NA	NA

Notes: *Statistically significant.
NA: Not applicable.

Discussion

Inflammation prevalence is high in HD patients. Chronic inflammation leads to malnutrition, atherosclerosis, cardiovascular diseases, serious morbidity and mortality. Inflammation consists as a result of uremic factors, such as decreased clearance and increased synthesis of proinflammatory cytokines, oxidative stress, AGE deposition, and by

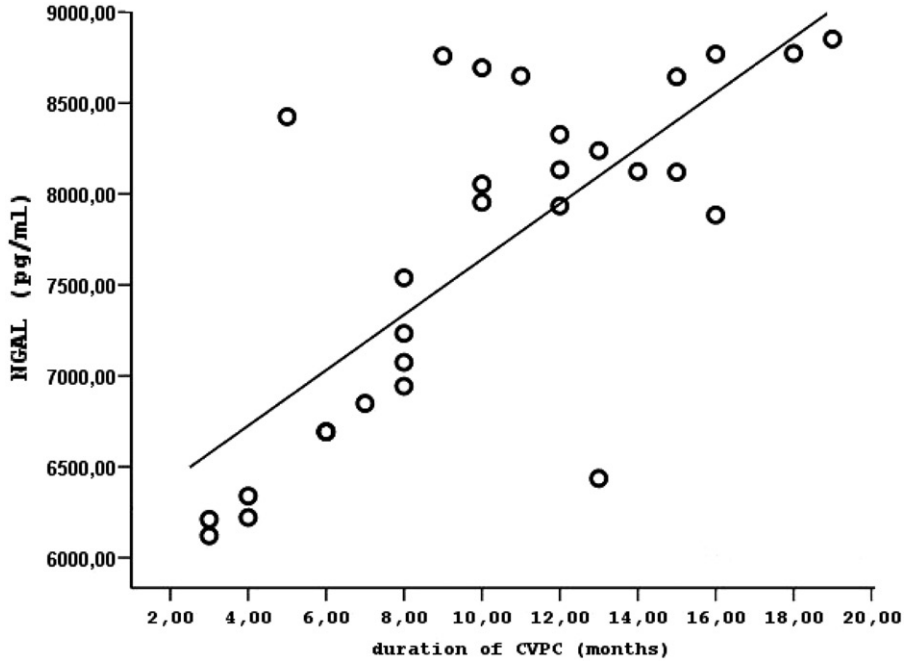

Figure 1. Correlation between serum NGAL levels and duration of CVPC in HD patients.

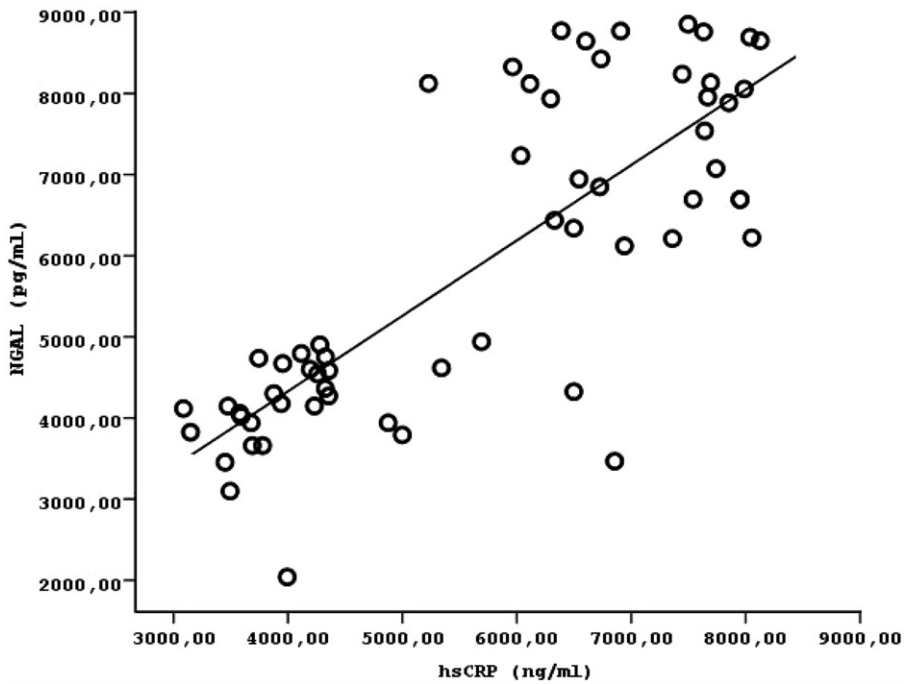

Figure 2. Correlation between serum NGAL and hs-CRP level in HD patients.

dialysis-related factors, such as membrane incompatibility, VA infection, endothelial exposure, and the presence of catheters or grafts.[13,14] Among the proinflammatory cytokines, IL-6 may have a central role in the pathophysiology of inflammation in patients with renal disease and HD.[15,16] A prospective study showed that both serum IL-6 and hs-CRP levels were higher in HD patients with CVPC than the patients with AVF and AVG.[17] Movilli et al.[18] reported that the highest serum CRP levels were found in the CVPC group ($n = 13$) when compared to AVF ($n = 48$), and AVG ($n = 18$) groups. AVG, CVPC, albumin levels, dialysis vintage, and age were found to be independent factors that affect CRP levels by the multivariant analysis. Our study demonstrated that not only serum IL-6 and hs-CRP but also TNF-α levels were the highest in patients with CVPC and our results are consistent with these studies. Recently, Karlsen et al.[19] demonstrated that NGAL was strongly induced by stimulation with TNF-α in the presence of IL-17, a proinflammatory cytokine. Furthermore, Arena et al.[20] showed that both IL-1β and TNF-α regulates the NGAL expression in polymorphonuclear granulocytes of HD patients. In addition, a few studies showed that relationships between NGAL and inflammation markers (hs-CRP, IL-6, TNF-α).[12,21] Our study has shown for the first time that HD patients with CVPC had significantly much higher NGAL and inflammation marker level than HD patients with AVF and

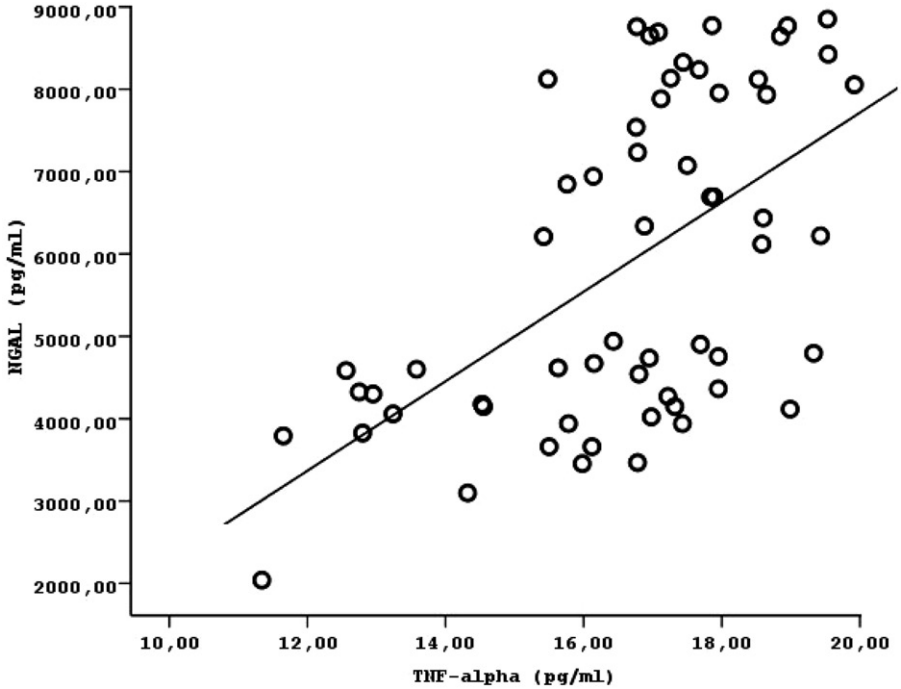

Figure 3. Correlation between serum NGAL and TNF-alpha levels in HD patients.

patients with stage 3–4 CRF. In spite of the fact that the use of CVPC increases due to increased age and comorbidities, our relatively young patients (50.98 ± 11.22) have less comorbidities but have relatively high proportion of use of CVPC. This is probably due to selection bias. In our study population, nephrolithiasis has relatively a high proportion, but it does not reflect the etiological role for whole CRF population.

Clinicians are aware of the practicality of NGAL that is a marker of kidney damage[11] and a predictor of the progression of CRF.[22] Indeed, NGAL level can also increase as a response to oxidative or thermal stresses apart from being a marker of renal insufficiency. It was shown that NGAL expression was increased in a mouse kidney that exposed to cold or heat stress. Furthermore, the *in vitro* investigation on human embryonic kidney cells (HEK293T) revealed the protective and anti-apoptotic role of NGAL against thermal stress. Also, the addition of recombinant NGAL to HEK293T, prior to cold stress or after heat exposure, protected those cells against the stress-induced apoptosis.[23] In this way, it was proven that NGAL behaved like a classical stress protein. From this point of view, the difference between patients with CVPC and AVF in HD can support that CVPC is more stress-inducing. Additionally, Liu et al.[24] reported that in systemic diseases with no obvious bacterial infection, serum NGAL levels was increased as acute phase response and can be used as an inflammation marker. A previous study demonstrated that extracorporeal circulation might increase the release of NGAL directly by immune cell activation.[25] However, stimulation of neutrophil degranulation during HD, might be another cause of increased NGAL levels.[26] As considered that HD treatment is a form of chronic stress and had an extracorporeal circulation, NGAL release in HD patients is an expected outcome.

Malyszko et al.[21] previously reported that serum NGAL levels were correlated with residual renal function, age, hs-CRP, IL-6, TNF-α, dialysis time, ferritin, urea, creatinine levels, and Kt/V_{urea} in HD patients. In this study, we demonstrated that there was no correlation among NGAL levels and age, WBC, duration of HD and Kt/V_{urea} but a positive correlation with TNF-α, hs-CRP, IL-6, ferritin levels and a negative correlation with albumin levels in each patient groups. In addition, residual renal function, degree of proteinuria, colorectal cancer, hyperuricemia may be associated with increased NGAL levels.[27–30] We did not investigate these situations. These are limitations of our study.

There is a negative correlation between serum albumin levels and acute inflammation markers because the albumins are negative acute phase reactants. Hypoalbuminemia is a risk factor for mortality and morbidity in HD patients.[31,32] Our study also showed that serum albumin levels were at the lowest value in the normal range in CVPC patients without a significant difference in Kt/V_{urea} among HD patients. The measurement of serum hs-CRP and IL-6 may help to distinguish the relative contributions of inflammation and malnutrition to the development of hypoalbuminemia. These findings support the idea that the presence of CVPC might increase both inflammation and malnutrition. But malnutrition has not been evaluated exactly in our study because of lack of bioimpedance usage.

Our study tested the hypothesis that HD patients with CVPC would have increased NGAL levels, as well as inflammatory biomarkers. Additionally, we hypothesized that NGAL levels would correlate with the elevation of inflammatory biomarkers. But this study has some important limitations. Firstly, it was executed in a single center and with relatively small groups. Secondly, due to the cross-sectional nature of the study, consecutive NGAL measurements could not be performed. Thirdly, the situation of vascular diseases and atherosclerosis in patients could not be evaluated by imaging methods.

We observed that elevated inflammatory markers in HD patients with CVPC correlated with NGAL levels, indicating

systemic inflammation. As a conclusion, in the absence of an organic cause of inflammation, the VA should always be suspected as inflammation cause. NGAL might be a useful and a non-invasive predictor for inflammation especially in HD patients with CVPC. AVF should be the first choice of VA in order not to enhance the existing inflammation in HD patients and usage of CVPC should be avoided as much as possible.

Declaration of interest

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