Plasma Gelsolin and Its Association with Mortality and Hospitalization in Chronic Hemodialysis Patients

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Key Words

Cytokines · Gelsolin · Hemodialysis · Inflammation · Uremic toxins · Free triiodothyronine · Hemodialysis · Mortality · Hospitalization

Abstract

Background: Human plasma gelsolin (pGSN) is an actin-binding protein that is secreted into the extracellular fluid, with the skeletal muscle and myocardial tissues being its major source. Depletion of pGSN has been shown to be related to a variety of inflammatory and clinical conditions. **Methods:** pGSN levels were prospectively determined in prevalent maintenance hemodialysis (HD) patients from 3 U.S. dialysis centers. Demographics (age, time since dialysis initiation, race, gender, body height and weight, comorbidities), inflammatory markers (C reactive protein, CRP; interleukin 6, IL-6), free triiodothyronine (fT3), and routine laboratory parameters were obtained. We performed Kaplan–Meier and Cox proportional hazard survival analysis for all-cause

and cardiovascular mortality, and recurrent event survival analysis for hospitalization. **Results:** We studied 153 patients; mean age was 60.5 ± 14.7 ; 52% were males. The mean pGSN level was $6,617 \pm 1,789$ mU/ml. In univariate analysis, pGSN was positively correlated with body mass index ($r = 0.2$, $p = 0.01$), pre-HD serum albumin ($r = 0.247$, $p = 0.002$), and pre-HD serum creatinine ($r = 0.381$, $p < 0.001$), and inversely with age ($r = -0.286$, $p < 0.001$), CRP ($r = -0.311$, $p < 0.001$), and IL-6 ($r = -0.317$, $p < 0.001$). In the adjusted analysis, the associations with CRP and creatinine were retained. pGSN levels tended to be lower in patients who died ($p = 0.08$). There was no association with all-cause or cardiovascular mortality, or all-cause hospitalization. Of note, fT3 was lower in patients who died ($p = 0.001$). **Conclusions:** Even though pGSN was inversely correlated with age, CRP and IL-6, suggesting that inflammation may influence pGSN, lower pGSN levels were not associated with hospitalization, all-cause and cardio-vascular mortality in this patient population.

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Introduction

While technical and clinical advances have improved morbidity and mortality in patients with chronic kidney disease (CKD), their outcomes continue to be poor, particularly in chronic hemodialysis (HD) patients [1–3].

Biomarkers such as inflammatory proteins are used frequently to identify patients at increased risk for adverse outcomes in a timely manner. Plasma gelsolin (pGSN) has been added to the growing list of biomarkers by showing its usefulness in predicting clinical outcomes in acute, severe [4–7] and chronic diseases [8–11]. GSN was first identified in cytoplasmic extracts as an actin-scavenger protein, which in the presence of ionized calcium disassembles actin filaments and increases cytosolic fluidity [12–14]. GSN was found in a variety of mammalian tissues [15–17]. pGSN is a highly conserved, high-molecular, actin-binding protein, mainly secreted by myocytes [18]. pGSN functions as an actin-sequestering protein. After binding to actin, the pGSN-actin complex is quickly cleared from the circulation; pGSN also contains inflammatory and immune reactions, thus protecting the host from further damage [19, 20]. Emerging data demonstrate that pGSN, in addition to scavenging actin, may also bind and modulate inflammatory mediators and exogenous bacterial lipids, as well as promote the disposal of actin and phagocytic uptake of bacteria in human plasma and mouse models [20, 21].

In summary, pGSN seems to play a key role in containing potentially overshooting host responses to sepsis, burns, trauma, and other clinical conditions. However, excessive actin exposure following extensive injury could lower pGSN levels, compromising containment of inflammation. The prognostic implications of low levels of pGSN before and after acute insults have been well documented [7, 22, 23]. More recently, pGSN has also been studied in CKD patients on HD [24, 25]. Previous studies have suggested that pGSN could be the link between malnutrition, inflammation, vascular calcification and mortality in HD patients [26, 27].

The correlation between low levels of free triiodothyronine (fT3), increased inflammation, and the presence of cardiovascular disease in the end-stage renal disease population has been firmly established [28–30]. Previous studies have not determined a causal relationship between fT3 and inflammation [30, 31]. However, there is persistent association between low triiodothyronine levels and increased risk of death in long-term HD patients [32, 33]. Measuring fT3 levels along with inflammatory

proteins such as interleukin 6 (IL-6) and C-reactive protein (CRP) may provide useful information in planning trials of fT3 replacement.

In this prospective multicenter study in chronic HD patients, we aimed to expand the body of knowledge by exploring associations between pGSN and inflammatory markers, hospitalization and survival.

Subjects and Methods

We conducted a prospective cohort study in 3 dialysis clinics of the Renal Research Institute (RRI). The baseline period lasted 1 month for each clinic, and data were collected from January 1, 2010 to April 30, 2010. Patient outcomes were recorded during a follow-up period of 34 months. The primary outcome was all-cause mortality; secondary outcome was all-cause hospitalization. Patients were categorized into tertiles of baseline pGSN levels.

We included HD patients aged 18 and above. Patients were excluded in cases of vascular access failure that would have prevented blood draws for pGSN determination. Within a month after providing informed consent, blood samples were drawn before (pre-HD) the mid-week HD session for the measurements of pGSN, IL-6, CRP, and fT3. Baseline clinical characteristics were collected on the first month of the study, and information on all-cause mortality and hospitalization events were retrieved on a monthly basis from medical records during the follow-up period.

The study was approved by the Institutional Review Board of Beth Israel Medical Center, New York, and conducted in accordance with the Helsinki Declaration. All patients gave informed consent.

Biochemical Measurements

pGSN level was determined using 2C4 Plasma Gelsolin ELISA kit (Critical Biologics Corporation, Cambridge, Mass., USA). fT3 was measured by direct chemiluminescence (ADVIA Centaur fT3 assay, Siemens, Deerfield, Ill., USA), CRP and complete blood count were measured by routine laboratory techniques; IL-6 was determined with the Quantikine ELISA kit (R&D, Minneapolis, Minn., USA) at Spectra Clinical Research (Rockleigh, N.J., USA).

Statistical Analysis

Continuous variables were reported as mean and SD, or as medians with interquartile range, depending on their distribution. Pearson or Spearman correlations between pGSN and inflammatory markers were performed depending on their distribution. For survival analysis, Kaplan–Meier survival curves were constructed and survival was compared between tertiles of pGSN using the log-rank test. For multivariate time-to-death analysis, Cox proportional hazards models were created. Recurrent event analysis for hospitalization was conducted. The proportional hazard assumption was verified through graphic (log–log survival plots) and statistical approaches (goodness of fit and t-dependent variable approaches). Stepwise regression analysis was performed to identify variables associated with pGSN level including variables with a *p* value <0.05. The variables used for adjustment were body mass index (BMI), diabetes, albumin, age, and IL-6.

Table 1. Demographics and baseline patient characteristics

Parameter	Total (n = 153)	Survivors (n = 124)	Non survivors (n = 29)	p value
Age, years	60.5±14.7	59.1±14.8	66.5±12.6	0.01
Females, %	74 (48.4)	59 (47.6)	15 (51.7)	0.69
Race, %				0.96
White	9 (5.9)	7 (5.6)	2 (6.9)	
Black	64 (41.8)	51 (41.1)	13 (44.8)	
Asian	7 (4.6)	6 (4.8)	1 (3.5)	
Hispanic	73 (47.7)	60 (48.4)	13 (44.8)	
BMI, kg/m ²	28.4 (23.7–32.5)	28.5 (23.7–32.4)	26.9 (23.6–33.5)	0.73
Diabetes, %	79 (51.6)	59 (47.6)	20 (69.0)	0.04
Cardiovascular disease, %	57 (37.3)	44 (35.5)	13 (44.83)	0.35
Hepatitis C infection, %	31 (20.3)	23 (18.6)	8 (27.6)	0.28
Dialysis vintage, years	2.4 (1.4–5.2)	2.4 (1.1–6.2)	2.5 (1.6–4.2)	0.78
Vascular access n (%)				0.006
AVF	108 (70.6)	94 (75.8)	14 (48.3)	
AVG	26 (17)	19 (15.3)	7 (24.1)	
Central venous catheter	19 (12.4)	11 (8.9)	8 (27.6)	
Albumin, g/dl	4.1 (3.9–4.3)	4.1 (3.9–4.3)	3.8 (3.6–4.0)	<0.001
Phosphorus, mg/dl	5.3 (4.3–6.4)	5.3 (4.4–6.3)	5.3 (4.2–6.4)	0.71
Creatinine, mg/dl	9.1±2.6	9.3±2.5	8.1±2.9	0.03
nPCR, g/kg/day	0.9 (0.8–1.1)	1.0 (0.8–1.1)	0.9 (0.7–1.0)	0.05
eKt/V	1.4 (1.3–1.6)	1.5 (1.3–1.6)	1.4 (1.3–1.5)	0.004
Hemoglobin, g/dl	11.9 (11–12.4)	11.9 (11.1–12.4)	11.9 (10.7–12.2)	0.48
Ferritin, µg/l	703 (399–956)	699.5 (391–981)	708 (590–919)	0.54
CRP, mg/l	6.8 (3.3–13.8)	6.1 (3.3–12.6)	9.5 (3.5–44.8)	0.08
IL-6, pg/ml	2.1 (2.1–5.5)	2.1 (2.1–5.1)	2.1 (2.1–11.7)	0.16
NLR	3.1 (2.2–4.1)	2.9 (2.2–4.0)	3.1 (2.3–4.3)	0.39
Triiodothyronine, pg/ml	2.4±0.4	2.4±0.3	2.2±0.4	0.001

Data are displayed as means ± SDs, medians (interquartile ranges) or n (%) as appropriate. p values resulted from chi-square tests.

nPCR = Normalized protein catabolic rate; eKt/V = equilibrated Kt/V; AVF = arterio-venous fistula; AVG = arterio-venous graft; NLR = neutrophil-to-lymphocyte ratio.

Two-sided p values <0.05 were considered statistically significant. Statistical analysis was performed with STATA/SE version 12.1 (Stata-Corp, College Station, Tex., USA).

Results

We studied 153 patients; 48% were females, mean age was 60.5 ± 14.7, 79 (51.6%) patients had diabetes, 57 (37.3%) had a history of cardiovascular disease, and dialysis vintage was 2.4 (1.4–5.2) years. The mean follow-up was 769 days. Patient characteristics are shown in table 1.

The mean pGSN level was 6,617 ± 1,789 mU/ml and the distribution is shown in figure 1. In univariate analysis, pGSN was positively correlated with BMI ($r = 0.200$, $p = 0.01$), pre-HD serum albumin ($r = 0.247$, $p = 0.002$), and creatinine ($r = 0.381$, $p < 0.001$), and inversely with

Fig. 1. Distribution of pre-HD pGSN levels.

Fig. 2. Kaplan–Meier survival curves in patients stratified by pGSN levels.

age ($r = -0.286$, $p < 0.001$), CRP ($r = -0.311$, $p < 0.001$), and IL-6 ($r = -0.317$, $p < 0.001$). In the adjusted analysis, the inverse relationship between CRP and pGSN was retained ($\beta = -23.8$ (-35.5 to -12.1), $p < 0.001$), as was the positive correlation with pre-HD serum creatinine ($\beta = 258.1$ (162.0 – 354.3), $p < 0.001$).

Mortality and Hospitalization

Twenty-nine patients (19%) died during the follow-up. The causes of death were cardiovascular ($n = 14$), infectious ($n = 5$), trauma ($n = 1$), and unknown ($n = 9$) with a median time to death of 380 days (283–554). Patients who died were older (67 ± 13 vs. 59 ± 5 years; $p = 0.01$), had a higher proportion of diabetes (69 vs. 47.6%; $p = 0.04$), and central venous catheter use (27.6 vs. 8.9%; $p = 0.006$), lower levels of albumin (3.8 (3.6–4.0) vs. 4.1 (3.9–4.3) g/dl; $p < 0.001$), lower equilibrated normalized protein catabolic rate (0.9 (0.7–1.0) vs. 1.0 (0.8–1.1) g/kg body weight; $p = 0.05$), lower equilibrated Kt/V (1.4 (1.3–1.5) vs. 1.5 (1.3–1.6); $p = 0.004$), and lower fT3 (2.2 ± 0.4 vs. 2.4 ± 0.3 pg/ml; $p = 0.001$), and a trend toward higher CRP (9.5 (3.5–44.8) vs. 6.1 (3.3–12.6) mg/dl; $p = 0.08$).

Pre-dialysis pGSN level tended to be lower in those patients who died ($5,995 \pm 1,789$ vs. $6,722 \pm 1,775$ mU/ml; $p = 0.08$). Figure 2 shows a similar survival probability between groups according to pGSN tertiles (chi-square = 3.4; log-rank $p = 0.17$). After adjustment for confounders, pGSN levels were associated with neither all-cause mor-

tality (table 2) nor cardiovascular mortality (HR 0.99, 95% CI 0.99–1.00; $p = 0.19$).

For hospitalization analysis, 7 patients with hospitalization related to kidney transplantation were excluded from the analysis, and 569 hospitalizations in 146 patients were recorded, 76 hospitalizations were related to infections (13.4%), and 193 (33.9%) to cardiovascular events, 23 (4.0%) to dialysis access dysfunction, and 277 (48.7%) to other causes (diabetes related, gastrointestinal complaints, electrolyte disturbances, pain, anemia, etc.). Neither in univariate (fig. 3) nor multivariate (table 3) analysis pGSN was associated with time to first all-cause hospitalization. In a subset analysis, pGSN was not associated with infection-related hospitalization (HR 1.00, 95% CI 0.99–1.00; $p = 0.92$; table 4).

Discussion

The key findings of our study were a positive correlation of pGSN with BMI, albumin and creatinine and a negative correlation with diabetes and inflammatory markers. pGSN was not associated with mortality and hospitalization.

pGSN acts as an actin-binding protein limiting the inflammation to local tissues, minimizing their damage. More recently, additional studies have suggested that it can act as an inflammatory mediator in different clinical scenarios [11, 21, 25, 34]. To the best of our knowledge,

Fig. 3. Kaplan–Meier analysis of time to first all-cause hospitalization.

Table 2. Univariate and multivariate analyses of predictors of all-cause and cardiovascular mortality

Parameter	Univariate analysis ^a		Univariate analysis ^b		Multivariate analysis ^c	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Age, years	1.03 (1.00–1.06)	0.02	1.03 (1.00–1.06)	0.05	1.02 (0.99–1.07)	0.21
Albumin, g/dl	0.25 (0.12–0.51)	<0.001	0.23 (0.10–0.51)	<0.001	0.35 (0.11–1.08)	0.07
Vintage, years	0.93 (0.83–1.05)	0.27			0.93 (0.78–1.10)	0.39
Cardiovascular disease	1.32 (0.63–2.74)	0.46			1.62 (0.57–4.64)	0.36
IL-6, pg/ml	1.02 (1.00–1.04)	0.05			1.03 (1.00–1.06)	0.05
pGSN, mU/ml						
>7,320.6	Ref				Ref	
5,624.9–7,320.6	1.85 (0.77–4.40)	0.17			0.75 (0.17–6.19)	0.95
<5,624.9	0.88 (0.32–2.42)	0.80			1.81 (0.17–3.37)	0.71
Diabetes mellitus	2.15 (0.98–4.73)	0.06			1.29 (0.45–3.72)	0.64
Catheter	3.92 (1.72–8.89)	0.001	4.01 (1.74–9.30)	0.001	2.77 (0.77–10.0)	0.12
Male	0.86 (0.41–1.78)	0.68			1.24 (0.43–3.57)	0.69
NLR	1.09 (0.96–1.25)	0.18			1.12 (0.94–1.33)	0.22
CRP, mg/l	1.02 (1.01–1.03)	0.003			1.01 (0.99–1.03)	0.09
Triiodothyronine, pg/ml	0.25 (0.09–0.69)	0.008			0.29 (0.07–1.26)	0.10

^a Univariate analysis for all-cause mortality.

^b Univariate analysis for cardiovascular mortality.

^c Multivariate analysis for all-cause mortality adjusted for age, gender, BMI, cause of end-stage renal disease, vascular access and biomarkers of inflammation.

NLR = Neutrophil-to-lymphocyte; Ref = pGSN reference group.

only 2 previous studies have investigated the relationship between pGSN and outcomes in CKD patients [25, 35]. We corroborated a previous study by Lee et al. [35] who showed in 150 incident HD patients that pGSN was directly associated with nutritional markers such as albu-

min and serum creatinine and inversely with age and inflammatory markers. In a larger sample, Lee et al. [35] performed a case–control analysis, where they found that pGSN levels were significantly lower in 114 patients who died within 1 year of dialysis initiation, than in 109 survi-

Table 3. Univariate and multivariate analyses of predictors of first all-cause hospitalization

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
Age, years	1.02 (1.00–1.03)	0.02	1.01 (1.00–1.03)	0.05
Albumin, g/dl	0.51 (0.34–0.78)	0.002	0.56 (0.37–0.87)	0.009
Vintage, years	0.97 (0.93–1.02)	0.30		
Cardiovascular disease	0.96 (0.66–1.41)	0.85		
IL-6, pg/ml	1.01 (0.99–1.02)	0.38		
pGSN, mU/ml				
>7,320.6	Ref			
5,624.9–7,320.6	1.11 (0.74–1.69)	0.61		
<5,624.9	1.15 (0.73–1.82)	0.54		
Diabetes mellitus	1.40 (0.98–2.02)	0.15		
Catheter	1.57 (0.99–2.49)	0.06	1.45 (0.88–2.39)	0.14
Male	0.98 (0.68–1.41)	0.92		
NLR	1.07 (1.00–1.16)	0.06		
CRP, mg/l	1.00 (0.99–1.01)	0.37		
Triiodothyronine, pg/ml	0.59 (0.35–0.99)	0.05		

NLR = Neutrophil-to-lymphocyte ratio; Ref = pGSN reference group.

vors. In contrast, we did not find a relationship between pGSN levels and all-cause or cardiovascular mortality. Of note, there are some differences in the populations. First, our study included only prevalent patients (median vintage of 2.4 years (1.4–5.2)), whereas Lee's study enrolled only incident patients. Other differences relate to race (Whites 6.9 vs. 53.1%), lower prevalence of catheter (12.4 vs. 58.3%), higher levels of serum albumin (4.1 g/dl (3.9–4.3) vs. 3.2 ± 0.6) and creatinine (9.1 ± 2.6 vs. 5.5 ± 2.6 mg/dl). Additionally, pGSN levels in our study were measured by ELISA as opposed to a functional fluorimetric assay used by Lee et al. [36], which may make a comparison difficult [37].

Cardiovascular disease is the most common cause of death in patients on chronic dialysis [3, 38, 39]. It is tempting to speculate that pGSN may be involved in the pathogenesis of cardiovascular disease because of its interaction with osteopontin and platelet function [40–42]. More recently, Chiou et al. [25] in 184 prevalent HD patients found that lower levels of pGSN were associated with the progression of aortic arch calcification, which has been associated with cardiovascular mortality [43, 44]. However, in our study, we did not find an association between pGSN and cardiovascular mortality. Interestingly, Chiou et al. [25] reported pGSN levels about one seventh of our lower tertile, and a lower BMI levels, which could be explained by the differences in the studied population.

Table 4. Multivariate analysis of predictors of infection-related hospitalization

Variable	HR (95% CI)	p value
Age, years	0.98 (0.95–1.01)	0.17
Albumin, g/dl	0.38 (0.17–0.82)	0.01
Vintage, years	1.05 (0.96–1.14)	0.29
Cardiovascular disease	1.76 (0.92–3.34)	0.09
IL-6, pg/ml	1.02 (0.99–1.06)	0.12
pGSN, mU/ml	1.00 (0.99–1.00)	0.92
Diabetes mellitus	4.92 (2.23–10.88)	<0.001
Catheter	4.17 (2.04–8.53)	<0.001
Male	0.93 (0.55–2.12)	0.82
NLR	0.88 (0.75–1.03)	0.10
CRP, mg/l	0.99 (0.98–1.01)	0.27
Triiodothyronine, pg/ml	1.03 (0.30–3.61)	0.96

NLR = Neutrophil-to-lymphocyte ratio.

Even though we did not intend to study fT3 outcomes, our results corroborate recent investigations [32, 45] showing an association of low fT3 levels and an increased risk of death in long-term dialysis patients.

The major limitation of our study is the fact that pGSN was measured only once. It would be important to study the predictive usefulness of repeated pGSN measurements. From the literature, it is noticeable that pGSN levels could differ between populations and vary by gen-

der, age, and ethnicity. It is also important to standardize the method of pGSN measurement.

In summary, we have shown that pGSN was directly associated with BMI, serum albumin and creatinine, and was inversely associated with age, CRP and IL-6. Patients who died during follow-up tended to have lower levels of pGSN, but after adjusting for confounding variables, pGSN was not associated with all-cause or

cardiovascular mortality. In addition, pGSN was not associated with all-cause and infection-related hospitalization.

Disclosure Statement

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