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Growth arrest-specific gene 6 (Gas6) levels are elevated in patients with chronic renal failure

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Abstract

Background. The TAM receptors (tyro3, axl and mer) and their ligands (vitamin K-dependent proteins—Gas6 and Protein S) are crucial modulators of inflammation, which may be relevant in chronic kidney disease (CKD). Gas6 and axl have multiple roles in mediating vascular atherosclerosis and injury, thrombosis and inflammation, yet nothing is known about the Gas6–axl pathway in humans with CKD. Given the prevalence of chronic inflammation and vascular disease in this population, we measured TAM ligands in patients with various levels of renal function.

Methods. Gas6 and protein S were quantified in the plasma by ELISA in three patient groups: end-stage renal disease on chronic hemodialysis (HD), CKD and normal controls.

Results. Significantly increased levels of Gas6 and protein S were found in CKD patients compared with normal controls (P < 0.01 and <0.001, respectively). In HD patients, Gas6 levels were elevated compared with controls (P < 0.001) and positively associated with low albumin (r = 0.33; P = 0.01), dialysis vintage (r = 0.36; P = 0.008) and IV iron administration (r = 0.33; P = 0.01). The levels of Gas6 rose with CKD stage and were inversely associated with estimated GFR (P < 0.0001).

Conclusions. Dysregulation of circulating Gas6 is associated with renal disease and inversely proportional to renal function. Low albumin and higher IV iron administration were associated with higher Gas6 levels, suggesting a possible connection between inflammation and oxidative stress mediated by iron. Protein S levels were also elevated in CKD patients, but the relevance of this finding needs to be further investigated.

Keywords: chronic kidney disease; dialysis; Gas6; inflammation; mortality; vascular disease

Introduction

Morbidity and mortality rates remain very high in chronic kidney disease (CKD). In CKD, the overall mortality rate is up to 30-fold higher than age-adjusted mortality in the general population [1–3]. Vascular disease, anemia, chronic inflammation and malnutrition are more prevalent in patients with CKD. Despite knowledge that CKD is associated with a state of chronic inflammation and with elevated levels of pro-inflammatory cytokines, both
contributing to increased vascular disease and cardiovascular mortality, we are far from a full understanding of the mechanisms that contribute to this diseased state [4–6]. Looking beyond traditional markers and identifying new mediators of chronic inflammation associated with vascular disease in CKD may be helpful in developing therapeutic interventions to reduce cardiac risk.

Gas6 is the protein product of the growth arrest-specific gene 6 and is a member of the vitamin K-dependent protein family. Various cell types express Gas6, including endothelial cells, vascular smooth muscle, leukocytes and platelets. A subfamily of tyrosine kinases—axl, tyro3 and mer—is also expressed on a variety of cells and serve as receptors for Gas6 [7]. Studies suggest that the Gas6/axl system imparts signals via the PI3K/Akt pathway, resulting in cell survival, proliferation, adhesion and protection from cellular death [8]. Gas6 and protein S also serve as bridges for mediating cell–cell interactions, binding both to TAM receptors and to phosphatidylserine residues exposed on activated platelets, injured endothelial cells and apoptotic bodies [9–12].

Numerous studies support Gas6 involvement in inflammation. In humans, Gas6 is elevated in sepsis, where increased plasma concentrations of Gas6 in patients with septic shock correlate with disease severity and increased mortality [13]. Human studies also demonstrate differences in protein S and Gas6 levels in disease conditions driven by autoimmunity compared with controls [14–16]. Finally, the TAM ligands and receptors modulate inflammation, regulating toll-like receptor signaling and proinflammatory cytokine signaling in macrophages and dendritic cells [8, 17]. Without the TAM receptors, animals develop unregulated immunity, autoimmunity and inflammation [12, 18, 19].

The role of Gas6 in vascular biology is complex. Gas6 promotes interactions between endothelial cells, leukocytes and platelets [9, 10, 20]. Animal and in vitro studies demonstrate a role for axl and Gas6 in endothelial cell activation, vascular smooth muscle cell (VSMC) proliferation, atherosclerosis, platelet aggregation and thrombosis [9, 21]. Gas6 and axl are upregulated by stimulated VSMC exposed to angiotensin II and reactive oxygen species in animals [22]. The Gas6/axl pathway has also been implicated in neointima formation after vascular injury in rats [23, 24]. Given these findings, it seems likely that in humans, the Gas6/axl pathway plays an important role in regulating adaptive responses to vessel injury [25–27].

The possible involvement of these TAM ligands has not been investigated in patients with chronic renal failure. The functions of the Gas6/axl system and its role in inflammation and vascular disease may be particularly relevant to CKD. Therefore, we sought to characterize Gas6 and protein S levels in individuals with varying levels of renal function.

Materials and methods

Subjects

This study was approved by the Temple University School of Medicine IRB. After written informed consent, blood samples were obtained from 53 patients with end-stage renal disease on chronic hemodialysis (HD), 72 patients with CKD and 23 healthy volunteers with no known medical history. Both CKD and HD groups were recruited from within the Temple University Nephrology practice. Inclusion criteria for CKD were evidence of proteinuria or renal dysfunction and no history of HD. For HD, patients were >6 months on HD. Exclusion criteria for both CKD and HD groups were patients on warfarin therapy.

Sample collection

In the CKD group, a single venous blood sample was obtained in the outpatient clinic. In HD, blood was collected both prior to and post-routine HD session. Blood samples were centrifuged at 3000 rpm and the plasma aliquoted and stored at −20°C or −80°C.

ELISAs

Gas 6 ELISA. ELISA plates (96 well) were coated overnight with a goat polyclonal antibody (R&D, AB885, Minneapolis, MI) at 2 µg/mL and washed with phosphate buffered saline (PBS) containing 0.05% Tween 20 (PBST) and blocked with 200 µL/well 3% bovine serum albumin (BSA) for 1 h. The plasma diluted 1:20 with PBS containing 1% BSA was added at 100 µL/well in duplicates, incubated for 2 h or overnight at 4°C and washed four times with PBST. Affinity-purified biotinylated goat polyclonal (R&D BAF885) was added at 1.0 µg/mL, incubated for 45 min at room temperature and washed with PBST. Streptavidin peroxidase (R&D DY998) diluted 1:200 with PBS containing 1% BSA was added and incubated for 45 min at room temperature. Substrate prepared according to the manufacturer’s instructions was added and color development monitored and terminated with 2 N H2SO4. The absorbance at 450 nm was read with a Versamark microplate reader (Molecular Devices, Sunnyvale, CA). The optical density for each sample was determined using Softmax software (Molecular Devices) and the concentration calculated by reference to a four-parameter logistical regression to a calibration curve using recombinant human Gas6 (R&D) TMB (3,3′,5,5′-tetramethylbenzidine, R&D).

Free protein S ELISA. Free protein S levels were quantified using the free protein S ELISA kit (Diagnostica Stago, Parsippany, NJ) according to the manufacturer’s instructions. Briefly, the heparinized plasma samples were diluted 1:20 in 1% BSA and duplicate samples applied to the precoated 96-well plate. Serial dilutions of purified protein S (Hematologic Technologies, Inc., Essex Junction, VT) starting at 20 µg/mL were used to construct a standard curve. The horseradish peroxidase (HRP) conjugated secondary antibody (50µL/well) was added and the plate was incubated at room temperature for 1 h. The plate was washed, developed with 200 µL/well of TMB substrate, the development terminated with 2 N H2SO4 and the absorbance at 450 nm was read using a Versamark microplate reader (Molecular Devices). The concentration was calculated using the Softmax software program.

Plasma PIVKA-II levels

The measurement of PIVKA-II was via an ELISA kit (Diagnostica Stago). The experimental procedure followed the manufacturer’s protocol. The ELISA utilizes a monoclonal antibody specific for PIVKA-II but without reactivity with native prothrombin as the capture antibody. Anti-prothrombin rabbit immunoglobulin conjugated with horse radish peroxidase is used to detect the antigen. Plasma prepared from ACD anti-coagulated blood and stored at −20°C were used in the assay. The PIVKA-II concentrations were calculated based on a standard curve fitted using a four-parameter curve fit calculated by the Softmax Pro analysis software (Molecular Dynamics, Sunnyvale, CA), and the concentrations of four standard plasma provided with the ELISA kit.

High-sensitivity C-reactive protein analysis

Plasma analysis for a high-sensitivity C-reactive protein (hsCRP) was performed utilizing hsCRP reagent and SYNCHRON LX® PRO System, UniCel® DxC 800 System(s) (Beckman Coulter Synchron systems).

Statistical analysis

Statistical Analysis System (SAS) biostatistical software and Graphpad (Graphpad Software, La Jolla, CA) were used for all statistical analyses. The data were expressed as the mean ± standard deviation. When comparing Gas6 and free protein S levels between control, CKD patients, HD patients and CKD stages, the method used for the group analysis was a one-way ANOVA. Since the Gas6 data were not normally
distributed, a rank transformation was applied prior to analysis. Pair-wise comparisons of group means were adjusted for multiple comparisons using the Bonferroni method to maintain an experiment-wide significance level of 0.05. When comparing the pre-dialysis and post-dialysis samples of Gas6, a Wilcoxon signed-rank test was performed. The Pearson and Spearman correlation coefficient were applied to establish the relationship between clinical and laboratory assessment data with Gas6 levels. A multiple correlation analysis was performed to test partial correlations with clinical and laboratory variables with Gas6 after adjustment for variables such as diabetes, years on dialysis, iron dosing and albumin. Other variables such as ferritin, PTH, phosphorus level and coronary artery disease were found to be non-significantly associated with Gas6 and were not entered into the adjusted model. A linear regression model was used to study the association between PIVKA II and Gas6 levels. A P < 0.05 was considered significant for all tests.

Results

Patient characteristics

The study subjects comprised 53 HD and 69 CKD patients, Stages I–V. The demographic, clinical and biochemical characteristics of all patients are listed in Tables 1 and 2. The subjects in HD and CKD were predominantly African Americans and are representative of the local dialysis population. In the CKD group, the majority of the patients had Stage III CKD (42%). The mean eGFR by MDRD was 40 mL/min.

Elevated Gas6 levels in chronic renal failure

Gas6 levels were significantly increased in HD and CKD patients compared with controls, with the highest levels observed in the HD group. The mean Gas6 level in normal subjects was 36.23 ± 18.33 ng/mL compared with 60% higher levels in CKD patients (58.34 ± 23.34, P < 0.01) and 3-fold higher mean levels in the HD group (102.8 ± 35.19 ng/mL, P < 0.001) (Figure 1). Due to the size of Gas6 (75 kDa), the plasma levels of Gas6 were unaffected by dialysis clearance as expected (121 ± 38.6 versus 101.3 ± 18.4, P = 0.10; n = 10) (Figure 2).

The distribution of Gas6 levels by CKD stage is depicted in Figure 3. Gas6 levels rose in early stages of CKD and progressively increased with advanced CKD (51.67 ± 16.12; 60.46 ± 17.96; 79.76 ± 38.09 for Stages III–V, respectively). In fact Gas6 was found to be significantly increased as a function of CKD stage (P < 0.0001). Further examination confirmed an inverse linear relationship between Gas6 levels and eGFR (r = −0.28; P = 0.02).

Clinical characteristics and Gas6 levels in HD patients

Clinical markers associated with chronic inflammation and mortality in HD patients were linked to Gas6. Using

Table 1. Main demographic and clinical characteristics of HD subjects

<table>
<thead>
<tr>
<th></th>
<th>HD subjects (n = 53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age in years (range)</td>
<td>59.3 (26.5–84.7)</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>34 (64%)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>52 (98)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Asian</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>23 (43.3)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>44 (83)</td>
</tr>
<tr>
<td>Presence of cardiovascular disease, n (%)</td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>10 (18.8)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>4 (7.5)</td>
</tr>
<tr>
<td>CVA</td>
<td>10 (18.8)</td>
</tr>
<tr>
<td>Mean creatinine [mg/dL (±SD)]</td>
<td>2.43 (1.89)</td>
</tr>
<tr>
<td>Hemoglobin [g/dL (±SD)]</td>
<td>11.7 (1.2)</td>
</tr>
<tr>
<td>Albumin [g/dL (±SD)]</td>
<td>3.76 (0.39)</td>
</tr>
<tr>
<td>Intact PTH [pg/mL]</td>
<td>436.9 (323.3)</td>
</tr>
<tr>
<td>Ferritin</td>
<td>733.3 (279.3)</td>
</tr>
<tr>
<td>Serum iron</td>
<td>53.4 (25.2)</td>
</tr>
<tr>
<td>Serum TBG</td>
<td>242.5 (54.2)</td>
</tr>
<tr>
<td>Percent transferrin saturation</td>
<td>23.8 (14.4)</td>
</tr>
</tbody>
</table>

Table 2. Main demographic and clinical characteristics of non-dialysis CKD subjects

<table>
<thead>
<tr>
<th></th>
<th>CKD subjects (n = 69)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age in years (range)</td>
<td>62.9 (32–85)</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>27 (39)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>50 (72.5)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>17 (24.6)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>2 (2.9)</td>
</tr>
<tr>
<td>Asian</td>
<td>0 (0)</td>
</tr>
<tr>
<td>CKD stage, n (%)</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>4 (6)</td>
</tr>
<tr>
<td>II</td>
<td>7 (10)</td>
</tr>
<tr>
<td>III</td>
<td>29 (42)</td>
</tr>
<tr>
<td>IV</td>
<td>18 (26)</td>
</tr>
<tr>
<td>V</td>
<td>11 (16)</td>
</tr>
<tr>
<td>Mean creatinine [mg/dL (±SD)]</td>
<td>40.4 (26.6)</td>
</tr>
<tr>
<td>Hemoglobin [g/dL (±SD)]</td>
<td>11.56 (2)</td>
</tr>
</tbody>
</table>
univariate correlation analysis in HD patients, cumulative monthly dose of intravenous iron given on HD was moderately associated with higher Gas6 levels. \((r = 0.33; P = 0.01)\). Conversely, the level of albumin was inversely associated with Gas6. \((r = -0.34; P = 0.01)\). In addition, patients who had been on dialysis for a longer period of time had higher Gas6 levels \((r = 0.36; P = 0.008)\). After accounting for multiple variables such as diabetes, years on dialysis and total monthly iron dosing, only dialysis vintage and iron dosing were found to be independently associated with Gas6 levels. There was a trend toward positive correlation of Gas6 levels with previous history of coronary artery disease \((r = 0.26; P = 0.06)\). However, hsCRP was not found to be significantly associated with Gas6 levels in our study \((r = 0.07, P = 0.69)\) (Table 3).

**Vitamin K status and Gas6 levels**

Gas6 is a vitamin K-dependent protein, with studies demonstrating vitamin K deficiency in both CKD and dialysis patients. To study the potential association between Gas6 levels and vitamin K deficiency, we utilized an established assay, the plasma levels of the liver protein induced by vitamin K absence II (PIVKA-II), to study vitamin K deficiency in our dialysis patients. In our HD population, 73% demonstrated elevated levels of PIVKA-II \((>2 \text{ ng/mL})\), indicating hepatic vitamin K deficiency. The mean value of PIVKA-II was 4.48 ng/mL (Figure 4A). By linear regression, Gas6 was not
associated with PIVKA-II levels ($r^2 = 0.1102$, $P = 0.11$ (Figure 4B)).

**Protein S levels in HD patients and non-dialysis CKD**

Higher free protein S levels were found only in CKD patients compared with controls, $8 \pm 2.5$ versus $5.04 \pm 1.39$ $\mu$g/mL, respectively ($P < 0.001$). For HD, the mean free protein S levels did not differ significantly from controls ($5.16 \pm 1.42$ versus $5.04 \pm 1.39$ $\mu$g/mL) (Figure 5). Although no association was found between free protein S levels and clinical parameters in HD patients (data not shown), free protein S levels were associated with increased creatinine in CKD patients ($r = 0.31$, $P = 0.009$).

**Discussion**

Our group is the first to demonstrate increased levels of Gas6 in HD and CKD patients compared with control subjects. Given the crucial role of Gas6 as a master regulator of cytokine production, particularly those linked with mortality such as IL-6, it is of interest that Gas6 levels were significantly elevated in HD patients compared with controls [8, 17, 28]. In HD patients, Gas6 levels were associated with cumulative monthly dose of iron, dialysis vintage and lower albumin—all known associated risk factors for chronic inflammation, accelerated vascular disease and increased mortality [29, 30]. Furthermore, increased Gas6 levels did not seem to be a direct product of the dialysis procedure itself. In many studies, contact of blood with the dialysis membrane has been blamed for initiating pro-inflammatory events. Our Gas6 plasma samples, however, were drawn pre-dialysis, and when post-dialysis samples were checked, no significant difference between pre- and post-dialysis samples were found. Furthermore, our finding that Gas6 is increased by CKD stage lends support to the idea that chronic renal failure in and of itself lends to its increased production, for reasons that are not yet clear.

As Gas6 is a vitamin K-dependent protein, the question as to whether increased levels of Gas6 may be caused by vitamin K deficiency in patients with renal failure cannot be fully answered by our current study [31, 32]. Our study did find increased PIVKA-II levels or vitamin K deficiency in the majority of our dialysis patients; however, no positive association between Gas6 and PIVKA-II levels were found. Our current assay used to measure Gas6 detects an area of the protein distinct from the Gla domain which is modified by carboxylation. Therefore, the assay will detect Gas6 regardless of carboxylation status, and should detect overall production of the Gas6 protein prior to its post-translational modifications. Certainly, the bioactivity of Gas6 may be compromised as carboxylation of the N-terminal region of the protein is required for its ability to bind phosphatidylserine residues. Such binding is relevant in the function of Gas6 in binding activated platelets and apoptotic bodies. On the other hand, binding to axl requires the C-terminal region of the Gas6 protein, which is not dependent on carboxylation.

The majority of CKD patients studied had Stage III–V disease. However, despite having small numbers of patients for each stage, we found significantly increased levels of Gas6 overall as a function of CKD stage. However, even at lower levels of eGFR, there is a wide distribution of Gas6 levels (data not shown), and some CKD patients have Gas6 levels that approach normal (Figure 1). Future studies are needed to determine why such different Gas6 levels may be seen at the same level of eGFR. A clear limitation of our current study is that our CKD cohort was not well characterized at the time samples were collected. In our study, the heterogeneity of the non-dialysis CKD patients and small numbers at each stage makes it difficult to determine what disease conditions, or nature of renal disease may drive abnormal expression of Gas6. As Gas6 and the TAM receptors axl and mer have been described in animal models of diabetic renal disease and nephrotoxic nephritis, it will be relevant to sort out whether Gas6 associates with different types of glomerular disease or whether Gas6 expression is driven by the presence of proteinuria [33, 34]. Indeed, Suh et al. [15] and Ekman et al. [16] demonstrated a role for both TAM ligands, protein S and Gas6, respectively, in reflecting disease activity in patients with lupus.

Several studies demonstrate the role of Gas6 and axl in mediating responses to vascular injury and in the development of atherosclerosis in animal models [10, 20, 21, 23, 24]. To date, there is only one human study that investigated Gas6 levels in patients with acute coronary syndrome without underlying CKD, with no association found [26]. In our study, there was a trend for HD patients with known CAD to have higher Gas6 levels. ($P = 0.06$) In part, this may be due to the number of study patients and the limitations of retrospective clinical information classifying patients with vascular disease. The presence of ‘silent’ or undocumented vascular disease in our patient population is certainly a possibility that could have weakened our ability to demonstrate an association. In addition, although one study demonstrated an association
of Gas6 levels with CRP in patients with critical limb ischemia, our study did not show such an association between CRP and Gas6 [35]. In part, this may be due to random sampling of our patient population, as opposed to sampling of patients with specific and active vascular disease. Other studies have demonstrated an association between plasma free protein S and presence of coronary heart disease and peripheral vascular disease in patients without underlying CKD [36, 37]. Interestingly, in our study, free protein S was significantly increased in CKD compared with controls, but was not found to be increased in HD patients. We have not yet tested whether levels of free protein S are altered by the dialysis procedure, and it remains unclear why protein S levels should be markedly different between the CKD and HD populations.

Finally, the mechanisms for elevation in circulating Gas6 levels in CKD patients not known, but the condition of chronic inflammation brought on by the development of chronic renal failure as well as by chronic dialysis raises many interesting possibilities. In vitro studies demonstrate both increased expression of Gas6 and axl expression in mouse mesangial cell and rat VSMC culture after exposure to angiotensin II and reactive oxygen species. Indeed, Fiebeler et al. [22] demonstrate wide renal tissue expression of Gas6 and axl in various types of human inflammatory glomerulonephritis. It seems unlikely, however, that local renal production of Gas6 and axl leads to increased amounts detected in the periphery, particularly in patients with advanced CKD. A more likely explanation for increased Gas6 levels in CKD patients is its role in endothelial cell function. Several lines of evidence demonstrate that Gas6 and its receptors are expressed by endothelial cells and leukocytes in conditions of inflammation and repair. In vivo studies in mice show that Gas6 is necessary to promote and accelerate the sequestration of platelets and leukocytes to injured endothelium [9, 10, 20]. It is well accepted that the endothelium in CKD is subject to particular stresses that are thought to play a role in accelerated vascular disease and increased cardiovascular mortality [30, 38, 39]. Oxidative stress, endothelial damage and structural disintegration of the endothelium leading to vascular microinflammation and dysfunction can wreak havoc both in the large vessels as well as in the glomerular capillaries, impacting both peripheral vascular disease and CKD progression.

Gas6 and axl can mediate potential proinflammatory signals, and this may be an especially relevant pathway for inflammatory disease conditions such as CKD. Basic studies demonstrate that the Gas6/axl pathway plays an important role in regulating innate immune. Exposure to potent maturation signals such as IFN-α and IL-6 causes axl upregulation on monocytes and differentiation into dendritic cells [40, 41]. In murine macrophages, TAM receptor signaling limits toll-like receptor production of proinflammatory cytokines through the induction of inhibitory proteins such as suppressors of cytokine signaling [8, 17, 42]. It is known that several proinflammatory cytokines such as IL-6, IL-1β and TNF-α are elevated in the blood of both non-HD CKD and HD patients [4–6]. It is possible that upregulation of TAM ligands and receptors in CKD is secondary to the development of chronic inflammation in renal failure.

In conclusion, this is the first report demonstrating increased expression of Gas6 in the plasma of patients with chronic renal failure. Based on what is known about Gas6, our findings indicate that the dysregulation of Gas6 protein could represent a novel inflammatory pathway contributing to human vascular disease in renal failure. Further studies are needed to examine how the Gas6–axl pathway may be regulated differently in patients with chronic renal failure and how derangements in this pathway may lead to vascular disease and chronic inflammation in CKD. Understanding the potential role and impact of the Gas6/axl pathway in CKD may help guide future therapies by targeting this pathway in patients with chronic renal failure.

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Conflict of interest statement. None declared.

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