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Biomarkers of Endothelial, Renal, and Platelet Dysfunction in Stage 5 Chronic Kidney Disease Hemodialysis Patients With Heart Failure

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Abstract

The aim of this study was to determine the role of endothelial, renal, and inflammatory biomarkers in the pathogenesis of heart failure (HF) in patients with stage 5 chronic kidney disease (CKD5) undergoing maintenance hemodialysis (HD). Plasma levels of biomarkers—kidney injury molecule 1 (KIM-1), N-terminal pro brain natriuretic peptide (NT-proBNP), glycated hemoglobin, neutrophil gelatinase–associated lipocalin, interleukin-l8,platelet-derived growth factor, platelet factor 4 (PF4), 25-OH vitamin D, parathyroid hormone (PTH), endothelin, and endocan—were measured in CKD5-HD patients at the Loyola University Ambulatory Dialysis facility. The HF (+) CKD5-HD patients, as compared to HF (–) CKD5-HD patients, exhibited significantly elevated NT-proBNP *(P* = .0194) and KIM-l *(P* = .0485). The NT-proBNP in HF (+) CKD5-HD patients was found to correlate with the levels of serum potassium (*P* = .023, *R* = −.39), calcium (*P* = .029, *R* =−.38), and PF4 (*P* = .045, *R* =−.35). The KIM-l in HF (+) CKD5-HD patients was found to correlate with PTH (*P* = .043, *R* = −.36) and 25-OH vitamin D (*P* = .037, *R* = .36). Elevated plasma NT-proBNP and KIM-l in CKD5-HD and HF (+) CKD5-HD patients suggest that natriuretic peptides and KIM-l may contribute to the pathogenesis of HF in CKD5-HD patients.

Keywords

chronic kidney disease stage 5; HF; hemodialysis; inflammatory biomarkers

Introduction

Heart failure (HF) is highly prevalent in patients with stage 5 chronic kidney disease (CKD5), with a prevalence of approximately 40%.[1] In one study, it was found that 31% of

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Declaration of Conflicting Interests

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the patients met the clinical criteria for HF and 25% of the patients who did not initially meet the medical criteria developed HF at a rate of approximately 7% per year.[2] In 2010, the direct and indirect US health-care cost of HF was $39.2 billion.[3] The HF in patients with CKD5 is characterized by left ventricular dilation and systolic and diastolic left ventricular dysfunction secondary to cardiac fibrosis and cardiomyopathy.[4] Patients with HF typically experience effort intolerance, fatigue, and edema.[5] Currently, the Kidney Disease Outcomes Quality Initiative guidelines recommend echocardiograms, 1 to 3 months after maintenance hemodialysis (HD) is initiated, in order to screen for HF due to its prevalence in patients with CKD5.[6]

The CKD5 is defined as having a glomerular filtration rate of 15 mL/min or less. At this stage, maintenance HD or kidney transplant is required to replace the function of the kidneys.[5] In CKD5, both fluid overload and nonhemodynamic factors play a role in the development of HF. Chronic pressure and volume overload in patients with CKD5 lead to left ventricular wall stress, ultimately contributing to cardiomyopathy and left ventricular failure.[6] Additionally, inappropriate activation of nonhemodynamic factors involved in oxidative stress, inflammation, fibrosis, the renin–angiotensin system, and collagen turnover leads to myocardial remodeling in HF.[5] The interplay of these nonhemodynamic factors in the disease process of HF in CKD5-HD is the focus of this project.

In patients with CKD5-HD, previous studies have shown that the uremic environment leads to platelet dysfunction due to hyporeactivity to bound agonists, impaired platelet–endothelial interactions, and decreased platelet granule contents. Endothelial dysfunction due to the toxic effects of uremia has been noted in these patients and is associated with increased ather-othrombotic risk.[7] Other studies have shown that dialysis membrane stress leads to platelet hyperreactivity, activation, and degranulation.[8,9] The platelet-derived growth factor (PDGF) is a growth factor released from the α-granules of platelets that functions in wound repair and angiogenesis.[10] The PDGF has a dimeric structure and is composed of A and B subunits. The pairing of subunits (AA, BB, AB) determines which PDGF receptor it can bind to.[11] The PDGF has recently been linked to cardiac fibrosis, hypertrophy, and cardiomyopathy in mice.[12] Additional studies have demonstrated that cardiac mast cells may cause atrial fibrillation through PDGF-A-mediated fibrosis in pressure-overloaded mouse hearts.[13] However, the role of platelet activation and platelet mediators in the pathophysiology of HF in CKD5-HD has not been well-studied. Platelet factor 4 (PF4) is also released by the α-granules of activated platelets and binds with high affinity to heparin and heparin-like molecules, decreasing antithrombin activity and promoting coagulation. Antibodies to the heparin-PF4 complex can be present, which when bound to the heparin-PF4 complex can lead to further platelet activation, vessel occlusion, and heparin-induced thrombocytopenia (HIT).[14] Measuring the levels of platelet degranulation could provide insight into whether the high frequency of HF in CKD5-HD patients is linked to platelet stress and dysfunction caused by maintenance HD and the uremic environment.

Cardiac, renal, and inflammatory biomarkers—kidney injury molecule 1 (KIM-1), N-terminal pro brain natriuretic peptide (NT-proBNP), neutrophil gelatinase–associated lipocalin (NGAL), and interleukin-18 (IL-18)—may also play a role in the pathogenesis of HF in CKD5-HD patients. The KIM-1 is a protein that is released by epithelial cells in the

proximal tubules of damaged kidneys during acute kidney injury and recently has been shown to have a role in tubular damage modulation and repair.[15] Studies have shown a relationship between increased urinary KIM-1 in elderly men and an increased risk of HF.[16] The role of KIM-1 in the pathogenesis of HF in CKD5-HD patients is not known. The NT-proBNP is secreted in response to excessive ventricular stretching leading to an increase in natriuresis and a decrease in vascular resistance.[17] The cardiac biomarker NT-proBNP has been extensively studied in CKD5-HD patients with HF, but due to the individual variability, its diagnostic and prognostic utility is limited in these patients.[18] However, the NT-proBNP still has utility in conjunction with other inflammatory and cardiac biomarkers to elucidate the pathogenesis of HF in CKD5-HD patients. Urinary NGAL is a marker of tubular damage and has been shown to be elevated in both acute and chronic kidney injury.[19] Studies have suggested that NGAL can be released from injured myocardium and be elevated in HF.[20] In animal models, elevated IL-18 levels may be associated with pressure overload and inflammatory states and may play a role in cardiac hypertrophy and remodeling.[20]

The aim of the study was to confirm the hypothesis that endothelial inflammation and dysfunction due to the uremic environment in CKD5-HD patients may contribute to the pathogenesis of HF. In addition, measuring endocan, endothelin, 25-OH vitamin D, and parathyroid hormone (PTH) will provide additional data to determine whether there is an interplay between endothelial dysfunction and HF in these patients. Endocan and endothelin-1 have both been found to be highly upregulated in CKD5.[21,22] Endocan is a molecule released by endothelial cells that plays a role in inflammation, cell adhesion, and endothelial cytoskeleton remodeling.[23] Endothelin is a vasoactive peptide that has been linked to HF and athero-sclerosis.[24] Vitamin D is involved in the downregulation of inflammatory mediators, and PTH functions as a regulator of vitamin D. Both hormones also regulate systemic calcium and phosphate levels.[25]

Profiling and correlating these cardiac and inflammatory biomarkers in CKD5-HD patients will allow for a better understanding of CKD5-mediated nonhemodynamic factors in the pathogenesis of HF.

Materials and Methods

Study Patients

Patients 18 years or older with CKD5 who underwent maintenance outpatient HD 3 times a week at Loyola University Medical Center (LUMC), Maywood, Illinois, were eligible for enrollment in the study.

Ninety patients (45 males and 45 females) were enrolled in the study. The patients ranged in age from 40 to 87 years, with a median age of 63.8 years. Following consent, plasma samples were collected prior to the dialysis session. This study was approved by the institutional review board. Table 1 describes the demographics of the CKD5-HD patients at LUMC outpatient dialysis center enrolled in this study.

Methods

Blood samples from 90 CKD5-HD patients had been collected during December 2014 and stored at −70°C until analysis. Venous blood samples were collected in 3.2% (0.109 mol/L) sodium citrate tubes immediately before each patient's dialysis session. The samples were centrifuged at 3000 rpm for 15 minutes, within 2 hours of blood draw, and the resultant plasma was divided into ten 100-μL aliquots and were frozen for storage at −70°C. Twenty-five male and 25 female plasma samples from healthy individuals were purchased from a biobank as control (George King Biomedical, Overland Park, Kansas). The control plasma samples were collected from nonsmoking, drug-free volunteers (aged 19–54 years, mean 33).

Determination of Biomarker Profile

The CKD5-HD and control plasma samples were used to profile KIM-1, NT-proBNP, NGAL, IL-18, PDGF, 25-OH vitamin D, PTH, endothelin, and endocan using commercial sandwich and competitive enzyme-linked immunosorbent assay kits and assays (R&D Systems, Minneapolis, Minnesota; RayBiotech, Norcross, Georgia; Hyphen Biomed, Neuville-sur-Oise, France). All reagents and standard solutions were prepared as directed from the assay manufactures. Patient and control plasmas were thawed and diluted according to the assay instructions.

Electronic Medical Record Chart Review

The patients' age, sex, diagnoses, comorbidities, medications, and dialysis laboratory test results were collected from their medical records using Epic electronic medical record. Any *International Classification of Diseases* diagnosis code that was carried through a patient's record was documented, which included HF, vascular disease, stroke, atrial fibrillation, and diabetes. Medication usage including statins, angiotensin-converting enzyme inhibitors, β-blockers, antiplatelet, aspirin, and insulin was recorded. Echocardiograms were reviewed to document whether there was any degree of left ventricular hypertrophy and the ejection fraction. Same day, predialysis blood samples were drawn as part of a monthly dialysis assessment and clinical data (serum potassium, chloride, CO_2, creatinine, calcium, blood pH, total protein, albumin, hemoglobin, platelet count, iron, ferritin, glycated hemoglobin [HbA_{1c}] transferrin, iron saturation, white blood cell count, glucose, and calcium phosphate) were made available in Epic charts.

Statistical Analysis

Biomarker and chart data were collected in Microsoft Excel and analyzed using GraphPad Prism v7 and Stata. The results were expressed as mean (standard deviation). Comparison between groups were evaluated using the nonparametric Mann-Whitney U test used for nonnormally distributed quantitative data. Correlation analysis was performed using the non-parametric Spearman test to correct for deviations from normality assumption. A P value less than .05 was considered statistically significant. The R values were generated to assess the strength of correlation graphs.

Results

Comparison of Biomarker Levels in the Control and CKD5-HD Groups

There were significant differences in the CKD5-HD patient plasma samples compared to control samples for endocan (2.18 [0.48] vs 1.81 [0.06] pg/mL; $P = .017$), NGAL (451.3 [9.7] vs 54.7 [1.8] ng/mL; $P < .0001$), vitamin D (21.89 [1.39] vs 31.14 [2.00] ng/mL; $P < .0001$), IL-18 (490.7 [33.4] vs 258.5 [15.6] pg/mL; $P < .0001$), NT-proBNP (12.94 [1.19] vs 0.1255 [0.0651] ng/mL; $P < .0001$), PTH (97.92 [17.17] vs 55.31 [6.273] pg/mL; $P = .0087$), PF4 (95.32 [3.72] vs 27.41 [2.09] ng/mL; $P < .0001$), and KIM-1 (0.705 [0.125] vs 0.059 [0.009] ng/mL; $P < .0001$). There were no significant differences in the CKD5-HD patient plasma samples compared to control samples for endothelin (2.80 [10.16] vs 2.70 [0.44] ng/mL; $P = .0507$) and PDGF (116.0 [18.1] vs 82.66 [16.05] pg/mL; $P = .4045$).

Comparison of Biomarker Levels in HF (+) CKD5-HD and HF (−) CKD5-HD Patients

All biomarkers and clinical data were tested for statistical differences between CKD5-HD patients with HF and CKD5-HD patients without HF. Significant differences were found for KIM-1, NT-proBNP, HbA_{1c}, systolic blood pressure (BP), and glucose (Table 2). All other biomarkers and laboratory data had no statistical differences.

Comparison of Biomarker Levels in HF (+) CKD5-HD and HF (−) CKD5-HD Patients Analyzed by Gender

An analysis was carried out to determine whether the levels of biomarkers were influenced by patient gender. All biomarkers and clinical data were tested for statistical difference between female CKD5-HD patients with HF and female CKD5-HD patients without HF. No statistical differences were found in the female population.

In males, KIM-1, NT-proBNP, HbA_{1c}, platelet, potassium, creatinine, calcium phosphate product, and glucose were all found to have statistical difference between CKD5-HD patients with HF and CKD5-HD patients without HF (Table 3). All other biomarkers and clinical data did not differ statistically.

Correlations of Biomarker Levels in HF (+) CKD5-HD Patients

The NT-proBNP in CKD5-HD patients with HF was found to correlate with K^+ ($P = .023$, $R = -.39$), Ca^+ ($P = .029$, $R = -.38$), and PF4 ($P = .045$, $R = -.35$). The KIM-1 in CKD5-HD patients with HF was found to correlate with creatinine ($P = .0175$, $R = -.41$), phosphate ($P = .002$, $R = -.51$), intact PTH ($P = .043$, $R = -.36$), calcium phosphate product ($P = .002$, $R = -.52$), and vitamin D ($P = .037$, $R = .36$).

Discussion

Our results demonstrated statistically significant differences between CKD5-HD patients and healthy controls for the majority of cardiac, renal, endothelial, and inflammatory biomarkers. These findings are consistent with data reported in other studies.[15–17,19–23,26,27] Patients with CKD have kidney damage, fluid overload, and an uremic environment. Therefore, it is reasonable that the biomarkers of inflammation (IL-18) and renal disease

(NGAL, KIM-1) are elevated. Elevation in cardiac (NT-proBNP) and endothelial biomarkers (endothelin, endocan) may be the result of the volume and pressure overload state in these patients, or intrinsic factors could be contributing to the cardiac and vascular dysfunction.

Our results have shown that the PDGF-BB was not significantly elevated in CKD5-HD patients compared to normal controls. This was expected to be elevated in CKD5-HD patients secondary to platelet activation and α-granule release. The lack of PDGF-BB elevation could be attributed to the fact that the plasma samples were collected pre dialysis and platelets may not have been stressed and activated. It was also previously shown that the uremic environment makes platelets hyporeactive and decreases the levels of their granule contents.[7] However, PF4, which is also released from the same a-granules from platelets, was found to be elevated. With this finding, it would be expected that PDGF-BB would also be elevated; therefore, it is difficult to definitively attribute the lack of statistical difference in PDGF-BB to one source. These findings suggest that PDGF and PF4 have independent release mechanisms in CKD5-HD patients. An increase in PF4 in CKD5-HD patients compared to normal controls is a novel finding. Platelet release of PF4 may be due to dialysis membrane stress on platelets from the previous session, the uremic environment, or heparin–PF4 complexed with antibodies binding to the platelet surface. Since these patients are heparinized, it would not be unusual to see elevated amounts of heparin-PF4 complexes in the blood.

It was found that there was elevated KIM-1, NT-proBNP, glucose, HbA_{1c}, and systolic BP in the CKD5-HD patients with HF compared to those without HF. The significance of the statistical difference in glucose is questioned due to the lack of standardization of fasting prior to dialysis among patients and the presence of glucose in the dialysate. Elevated plasma levels of NT-proBNP and KIM-1 in CKD5-HD patients with HF suggest that natriuretic peptides and KIM-1 may contribute to the pathogenesis of HF in CKD5-HD patients. Elevated NT-proBNP in CKD5-HD further supports previous studies demonstrating its potential diagnostic and prognostic utility.[17] Serum levels have value in our study to help correlate NT-proBNP with other biomarkers. The KIM-1 is a marker of acute kidney injury, but in our study, it was found to be elevated in patients with CKD and HF. Previous work has suggested that elevated KIM-1 levels may increase the risk of the development of HF. In our study, it was not possible to determine whether the elevation of KIM-1 in patients with HF is the result of volume and pressure overload or if it's a nonhemodynamic factor contributing to the remodeling and dysfunction of the myocardium. Elevated systolic BP confirms the state of fluid overload in patients with HF.

In male HF (+) CKD5-HD patients, there is a decreased platelet count with a mean of 146 × 10^3/μL, which is defined as mild thrombocytopenia (<150 × 10^3/μL). Since there were no statistical differences in the hematocrit or leukocyte levels, this makes hemodilution a less likely explanation for the thrombocytopenia. As described above, thrombocytopenia could be predicted for CKD5-HD patients due to recurrent heparinization leading to HIT. However, HIT occurring in CKD5-HD has not been reported in the literature. Any source of platelet activation could potentially lead to degranulation and platelet exhaustion leading to a decreased platelet count. Interestingly, PDGF-BB and PF4, 2 biomarkers released by activated platelets, were not elevated in HF (+) CKD5-HD patients compared to HF (−)

patients. The PDGF-BB had a positive correlation with platelet count, suggesting that as platelet count decreases, so does the levels of PDGF-BB in systemic circulation. Female HF (+) CKD5-HD patients did not exhibit any statistically significant differences in biomarkers compared to HF (−) CKD5-HD. The factors behind these gender-based differences may be androgen mediated but are unclear at this time.

In HF (+) CKD5-HD patients, it was found the NT-proBNP had a negative correlation with PF4. Although the levels of NT-proBNP do not directly correlate with the severity of HF in these patients, its correlation with PF4 may suggest a role for PF4 in the development of HF in these patients. The KIM-1 in HF (+) CKD5-HD patients was found to correlate positively with vitamin D and negatively with creatinine, intact PTH, and calcium phosphate product. The interplay with KIM-1, intact PTH, and vitamin D is more complex and less understood. Increased vitamin D production in the proximal tubule cells could lead to further stress of the proximal tubule endothelium and as a result increased KIM-1 levels. The complexity of these correlations will require the focus of future studies.

Limitations

One of the limitations of this study was the lack of age-matched controls. The age range for the controls was 19 to 54 years, with a mean age of 33 years, while CKD5-HD patients had a range of 40 to 87 years, with a mean age of 64 years. It was therefore not possible to control for age-related elevation in the biomarkers studied. Another limitation of this study is that the patient plasma samples were only collected pre dialysis. Some of our hypotheses were based on stress occurring during dialysis. Therefore, these patients had 2 to 3 days to recover from the dialysis membrane stress. Further studies could look at postdialysis samples and potentially compare them to predialysis samples.

Conclusion

Elevated plasma NT-proBNP and KIM-1 in all of the CKD5-HD patients and CKD5-HD patients with HF suggests that natriuretic peptides and KIM-1 may contribute to the pathogenesis of HF in CKD5-HD patients. Elevated NT-proBNP further supports previous studies demonstrating NT-proBNP's potential diagnostic and prognostic utility. Previous studies have demonstrated that there tend to be elevated urinary KIM-1 levels in CKD5-HD patients, but elevated plasma KIM-1 in CKD5-HD patients with HF may contribute to cardiac remodeling and dysfunction. Further studies are required to clarify the role of this biomarker in the pathogenesis of HF in CKD5-HD patients.

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Table 1.

CKD5-HD Patient Demographics at LUMC Outpatient Dialysis Center.

Parameter	# of Patients (% of Total)
Total CKD5-HD patients	90
HF (+) CKD5-HD patients	33 (37%)
Female CKD5-HD patients	17(19%)
Male CKD5-HD patients	16 (18%)
Age, range (mean)	40–87 years (63.8 years)
β-Blockers	53 (58%)
ACE inhibitors	18 (20%)
Aspirin	42 (46.7%)
Insulin	36 (40%)
Antiplatelets	12 (13%)
Statins	52 (57.8%)
Atrial fibrillation	19 (21.1%)
Anticoagulants	22 (24.4%)

Abbreviations: ACE, angiotensin-converting enzyme; CKD5-HD, stage 5 chronic kidney disease hemodialysis; HF, heart failure; LUMC, Loyola University Medical Center.

Table 2.

Comparison of Biomarker Levels in HF (+) CKD5-HD and HF (−) CKD5-HD Patients.

Marker	HF (+) Group	HF (−) Group	P
KIM-I, ng/mL	0.920 (0.279)	0.580 (0.113)	.0485
ProBNP, ng/mL	16.58 (2.11)	10.84 (1.37)	.0194
HbA_{Ic}, %	7.20 (0.32)	6.26 (0.24)	.0444
Systolic BP, mmHg	133.9 (4.2)	125.2 (2.7)	.0379
Glucose, mg/dL	160.2 (10.0)	132.2 (6.4)	.0154

Abbreviations: BP, blood pressure; CKD5-HD, stage 5 chronic kidney disease hemodialysis; HbA_{Ic}, glycated hemoglobin; HF, heart failure; KIM-1, kidney injury molecule 1; proBNP, pro brain natriuretic peptide.

Table 3.

Comparison of Biomarker Levels in Male HF (+) CKD5-HD and HF (−) CKD5-HD Patients.

Marker	Male HF (+) Group	Male HF (−) Group	*P*
KIM-I, ng/mL	1.27 (0.539)	0.656 (0.198)	.0121
proBNP, ng/mL	19.7 (3.53)	10.6 (1.7)	.0469
HbA_{1c}, %	7.56 (0.439)	5.99 (0.356)	.0202
PLT, × 10^3/mL	147(16.6)	175 (8.22)	.0476
K^+, mEq/L	4.38 (o.171)	4.83 (0.0922)	.0218
Creatinine, mL/min	8.79 (0.972)	11.6 (0.661)	.0152
Calcium phosphate, mg^2/dL^2	48 (2.57)	56.1 (2.55)	.0289
Glucose, mg/dL	169 (l3.6)	132 (9.9)	.0242
EGFR, mL/min	7.63 (0.948)	5.31 (0.318)	.0401

Abbreviations: CKD5-HD, stage 5 chronic kidney disease hemodialysis; EGFR, estimated glomerular filtration rate; HbA_{1C}, glycated hemoglobin; HF, heart failure; K+, serum potassium; KIM, kidney injury molecule; PLT, platelets; proBNP, pro brain natriuretic peptide.