

# Arterial-renal Syndrome in Patients with ESRD, a New Disease Paradigm

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## Abstract

**Background:** Patients with end-stage renal disease (ESRD) often present with an increased risk of cardiovascular disease. Conditions of compromised cardiovascular health such as atrial fibrillation (AFIB) and peripheral arterial disease (PAD) may alter biomarker levels in a way that reflects worsening ESRD. This study profiled biomarkers and laboratory parameters of endothelium dysfunction in patients with ESRD, categorized by additional AFIB and PAD conditions.

**Methods:** Citrated blood samples were collected from 95 patients with ESRD. Biomarker levels were measured from plasma samples using sandwich ELISAs, including tissue plasminogen activator (tPA), D-dimer, and nitrotyrosine. Lab parameters, including BUN, calcium, creatinine, parathyroid hormone, phosphate, alkaline phosphatase, ferritin, transferrin, and total iron capacity, and patient comorbidities were obtained from patient medical records. The comorbidities were determined through provider notes, and evidence of applicable testing.

**Results:** 14.89% of patients were found to have atrial fibrillation (n = 14), 30.85% of patients were found to have peripheral arterial disease (n = 29), and 6.38% of patients were found to have both peripheral arterial disease and atrial fibrillation (n = 6). When compared to patients with only ESRD, patients with ESRD and PAD showed elevated levels of D-Dimer (p = .0314) and nitrotyrosine (p = .0330). When compared to patients with only ESRD, patients with atrial fibrillation showed elevated levels of D-Dimer (p = .0372), nitrotyrosine (p = .0322), and tPA (p = .0198).

**Conclusion:** When compared to patients with just ESRD, patients with concomitant PAD had elevated levels of Nitrotyrosine and D-dimer; while patients with concomitant Afib had elevated levels of nitrotyrosine, D-dimer, as well as tPA.

## Keywords

atrial fibrillation, bioassay, biomarkers, bleeding, cardiology, peripheral arterial disease

## Introduction

### Background

Chronic kidney disease (CKD) is a slowly progressive disease state of the kidney that is characterized by a loss of function that may lead to total loss of function known as end-stage renal disease (ESRD). CKD affects more than 20 million people in America, and over 500 000 Americans have had progression into ESRD.<sup>1</sup> Moreover, CKD/ESRD creates an immense social and economic burden both on the personal level of the patient as well as the health care system at large, by requiring a complex level of specialist care and chronic management by trained personnel.<sup>2</sup> In fact, the overall cost of CKD accounts for 1.3% of our healthcare budget and what's more, 13% of which is unrelated to the care of CKD alone but instead associated comorbid conditions.<sup>3</sup> The financial burden

of CKD/ESRD and its comorbid condition is paralleled by a health-care related burden that is reflected in the high level of mortality even in the setting of dialysis use.<sup>4</sup> Furthermore,

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over half of the deaths in patients on dialysis with CKD/ESRD are attributed to cardiovascular related death and some studies have suggested that a mild to moderate elevation in serum creatinine is associated with increased rates of mortality from cardiovascular disease.<sup>5</sup> An example of cardiovascular disorder is atrial fibrillation in which an ectopic foci most commonly around the pulmonary veins become independent of the SA node. Atrial fibrillation has a prevalence of 15% to 20% in patients with CKD/ESRD, and thus is a significant subtype of cardiovascular disease to approach.<sup>6</sup> Indeed, CVD is a comorbid condition that worsens prognosis for patients with CKD and must be handled as well as recognized early on in its disease course to limit its potential severity.

*Cardiovascular disease and CKD/ESRD.* First noted in 1836,<sup>7</sup>

“It is observable, that the hypertrophy of the heart seems, in some degree, to have kept pace with the advance of disease in the kidneys; for in by far the majority of cases, when the heart was increased, the hardness and contraction of the kidney bespoke the probability of long continuance of the disease.” – Bright

It was suggested early in the understanding of CVD and CKD that the retention of certain substances within the blood due to altered filtration ability in the kidney rendered an alteration in the propulsive properties of the heart.<sup>8</sup> While elucidated early in the 20<sup>th</sup> century, this same idea has been since proven to be true that outside of traditional risk factors for CVD including hypertension, hyperlipidemia as well as long standing diabetes, there is an array of nontraditional factors that lead to CVD in patients with CKD.<sup>9,10</sup> While naïve to assume only one process is to contribute to the development of CVD in CKD, an important pathology to consider is endothelial cell dysfunction. Endothelial cell dysfunction has been measured through flow mediated vasodilation and inflammatory mediators, as well as more direct means through the observation of endothelial-derived microparticles released after significant damage.<sup>11</sup> Indeed, it has been shown that albuminuria (both micro and macro) is an indicator of endothelial cell dysfunction, is a hallmark feature of CKD.<sup>12</sup> Thus, endothelial cell dysfunction may be a shared initial step in the development of CVD both with CKD and without. Many causes of endothelial cell

dysfunction in patients with CKD have been revealed in the literature and include apolipoprotein abnormalities, elevated levels of asymmetric dimethyl-L-arginine (ADMA) and elevated levels of homocysteine.<sup>11</sup> Moreover, secondary hyperparathyroidism, a metabolic consequence of long-standing CKD, has been shown to cause left ventricular hypertrophy, interstitial fibrosis within the myocardium, as well as thickening of the intramyocardial arterioles.<sup>13</sup> These microsystem alterations are made worse by the activation of local macrosystems such as the renin-angiotensin-aldosterone system (RAS) which creates alterations in systemic vascular resistance, as well as the endothelin-1 system which has been shown to correlate closely with left ventricular remodeling.<sup>14</sup> These reasons among many others (many of which are not well understood) contribute to the link between CVD and CKD, and the close association between the two disease processes has facilitated the need to name a combined pathological state that encompasses that final state these patients find themselves. This disease process has been colloquially named cardiorenal syndrome.

*Cardiorenal syndrome.* As discussed earlier, a large proportion of patients with CKD/ESRD present with concomitant CVD that is atypical when compared to the normal case of CVD exacerbation. The exact definition of cardiorenal syndrome varies, however it is understood to either be an exacerbation of heart failure secondary to renal failure, or an exacerbation of renal failure secondary to heart failure. In either case, it is now accepted that cardiorenal syndrome can fall into 1 of 5 categories (table 1).<sup>15</sup> Most notably, cardiorenal syndrome type 4 describes a state of CKD/ESRD whereby the filtration capacity of the kidneys is altered leading to progressively worsening cardiac function over time. With that being said, these definitions are mere attempts to describe a pathological sequence of events that leads to a combined cardiac-renal disorder, when in reality, simultaneous mechanisms that predominate in any one type of cardiorenal syndrome are occurring at all times. These mechanisms can cause hemodynamic alterations and systemic inflammation.

Firstly, hemodynamic alterations can occur in both CKD and chronic heart failure (HF) that alter central venous and intraabdominal pressure. The altered pressure gradients in both of these conditions have been shown to increase central venous pressure, intraabdominal pressure, and in severe cases, lead to a condition known as abdominal compartment syndrome. In any stage of congestion, elevated renal vein pressures result in compromised perfusion and blood flow through the kidney that has been shown to reduce the glomerular filtration rate (GFR) and decrease the kidney's functional capacity.<sup>16</sup> In addition, dysregulation, and faulty activation of the RAAS system leads to maladaptive changes in vessel properties as well as system wide hemodynamics. Interestingly, the activation of RAAS not only can affect the functional capacity of the heart through remodeling, but on a more microscopic level the activation of endothelin-1 through this system leads to pro-fibrotic and pro-inflammatory changes in the kidneys.<sup>17</sup> Furthermore,

**Table 1.** Description of subtypes of cardiorenal syndrome

Cardiorenal syndrome type 1	Abrupt worsening of cardiac function leading to acute kidney injury
Cardiorenal syndrome type 2	Chronic abnormalities in cardiac function leading to progressive kidney injury
Cardiorenal syndrome type 3	Abrupt worsening of kidney function that leads to cardiac dysfunction
Cardiorenal syndrome type 4	Chronic kidney disease that leads to progressive cardiac dysfunction
Cardiorenal syndrome type 5	Systemic condition that causes dysfunction in both cardiac and renal function

the end-organ effects Angiotensin II (AGII) result in pathologic activation of TGF-beta that causes cardiac hypertrophy, as well as activation of oxidative stress pathways.<sup>18</sup>

Secondly, systemic inflammation in the form of oxidative stress, endothelial cell dysfunction, and circulation of maladaptive cytokines has been shown to play a large role in CS due to the direct effects of decreased tissue perfusion and venous congestion.<sup>19</sup> Specifically, in patients with cardiorenal syndrome type 1, elevated levels of IL-6, myeloperoxidase, nitric oxide, and endogenous peroxidase have been consistently found indicating the presence of a systemic wide inflammatory state.<sup>20</sup> These cytokines among others that have been found to be elevated in patients with cardiorenal syndrome promote apoptotic changes in the kidneys, structural changes in the heart, and systemic wide inflammation that is deleterious to the health of endothelial cells.<sup>18,21</sup>

While understood to be a disorder of altered hemodynamics, compromised cardiac function and reduced kidney function, there seems to be a large contribution at the microscopic levels of inflammatory mediators that worsen the disease state in these patients. Many of these pathophysiologic processes are understood to result from venous congestion and “back flow” from the heart into the kidneys. While cardiorenal syndrome is currently being better recognized throughout the medical community, there seems to be a lack of attention towards the inflow side of concomitant CVD and CKD. Namely, peripheral arterial disease and its contribution to a potential deleterious state that the authors of this manuscript have named “arterial-renal syndrome (ARS)”.

**Arterial-Renal syndrome.** Peripheral artery disease (PAD) is a state of chronic inflammation and atherosclerotic occlusion of the peripheral vasculature. This devastating disease has a prevalence of 8.5 million people in America, which the highest incidence among African Americans.<sup>22</sup> PAD alone is associated with other cardiovascular disorders, and recent studies have shown that patients with PAD who experience stroke or MI have a poorer prognosis than patients who experience these conditions alone.<sup>23</sup> Moreover, PAD is of particular relevance in patients with CKD as according to the US renal data system, the prevalence of patients with CKD and PAD (25%) is higher than that of myocardial infarction (9.3%) and stroke (16.1%).<sup>24</sup> While the exact interconnection between PAD and CKD/ESRD is outside of the scope of this manuscript, it has been well studied that having concomitant PAD and ESRD leads to worsening kidney function more rapidly, higher risk of lower extremity amputation as well as increased risk of developing any cardiovascular disorder.<sup>25</sup> Indeed, with such a large prevalence and such a higher degree of morbidity as well as mortality in patients with PAD and CKD, there seem to be subtle similarities between these patients and patients with cardiorenal syndrome. While cardiorenal syndrome is predominantly a disease that arises ultimately from venous congestion, compromised renal function in patients with PAD have a disease of arterial supply that limits perfusion to the kidneys. In a similar way, this results in alterations of the local inflammatory environment and may promote fibrotic

pathways that result in chronic changes in the kidneys. In turn, as kidney function deteriorates, retention of maladaptive substances in the vasculature can further compromise the arterial system worsening the existing peripheral arterial disease. These mechanisms have been explored and confirmed in the literature through elucidating elevated levels of pro-inflammatory biomarkers in patients with PAD and ESRD.<sup>24</sup> With that being said, there is limited research into direct comparisons between levels of inflammatory biomarkers in patients with CKD and concomitant CVD and PAD. Thus, our team set out to profile biomarkers, that have been traditionally studied to indicate states of endothelial cell dysfunction, oxidative stress, and inflammation, in patients with ESRD/CKD alone compared to patients with ESRD/CKD and concomitant PAD as well as atrial fibrillation (CVD). Specifically, D-dimer, MDA, Nitrotyrosine, vWF, tPA, eNOS, Nitric Oxide (total), PAI-1, and hsCRP.

## Materials and Methods:

### Study Design

Citrated blood samples from 95 patients with ESRD undergoing hemodialysis were collected during their dialysis treatments. Control samples, comprised of plasma from 50 health volunteers, were obtained from George King Biomedical (Overland Park, KS). The study cohort as well as the control cohort were stored at  $-70$  degrees Celsius in the storage facilities in the Center for Translational Research and Education (CTRE) at Loyola University Medical Campus. The samples were tested using commercially available ELISA assays for the above listed biomarkers. These samples were analyzed in the Hemostasis and Thrombosis laboratories. A chart review was conducted of the 95 dialysis patients to obtain relevant past medical history and available laboratory data. PAD was defined as clinical evidence of compromised arterial flow as well as a history of an ABI  $<.9$ .

### Statistical Analyses

Demographical data were analyzed via descriptive statistics. GraphPad Prism software was used in performing statistical analyses, such as one-way ANOVA, Pearson's correlation coefficient, Sidak's multiple comparisons, and calculation of means and standard error of the mean. All conducted statistical analyses were 2-sided with an  $\alpha$  of .05.

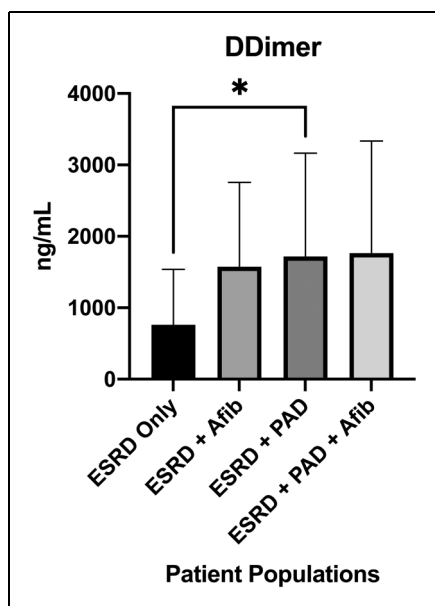
## Results

Of the 94 patients with ESRD, 14.89% of patients were found to have atrial fibrillation ( $n = 14$ ), 30.85% of patients were found to have peripheral arterial disease ( $n = 29$ ), and 6.38% of patients were found to have both peripheral arterial disease and atrial fibrillation ( $n = 6$ ). When compared to patients with only ESRD, patients with ESRD and PAD showed elevated levels of D-Dimer ( $p = .0314$ ) and nitrotyrosine ( $p = .0330$ ). When compared to patients with only ESRD, patients with atrial fibrillation showed elevated levels of D-Dimer ( $p =$

.0372), nitrotyrosine ( $p = .0322$ ), and tPA ( $p = .0198$ ). In addition, MDA was found to be elevated in patients with ESRD and atrial fibrillation more than ESRD alone, ESRD and PAD, as well as ESRD with both PAD and atrial fibrillation. vWF was found to be highest in patients with ESRD and atrial fibrillation, and lowest in patients with ESRD and both atrial fibrillation as well as PAD. tPA was also found to be highest in patients with atrial fibrillation when compared to other cohorts, and finally PAI-1 as well as eNOS were found to be highest in patients with ESRD alone. In addition, spearman correlation coefficients were used to determine correlations between associated biomarkers which resulted in statistically significant correlations between MDA and hsCRP ( $p = .024, -.84$ ) in patients with concomitant ESRD and atrial fibrillation (Figure 1).

## Discussion

As discussed previously, chronic CKD/ESRD commonly results in comorbid conditions such as CVD and PAD, that together create a new pathophysiological state that is characterized by a cycle of worsening cardiovascular and renal function (Image 1). Cardiorenal syndrome has been well described in the literature and while the exact pathophysiology has not been elucidated, it is now understood that in addition to macroscopic hemodynamic changes, alterations in the microenvironment of both the heart and kidney have large contributions to the end stages of the disease. In our study, we have used patients who have chronic atrial fibrillation as a proxy for cardiorenal syndrome as these patients have a clinical behavior. Our results revealed elevated levels of D-Dimer, MDA, Nitrotyrosine,



**Figure 1.** Analysis of biomarker levels in patients with ESRD as well as concomitant CVD. Statistically significant elevations were seen in patients with ESRD and CVD when compared to ESRD alone for D-Dimer, Nitrotyrosine, and tPA. In addition, elevations were found in MDA, vWF, and hsCRP. Patients with ESRD alone were found to have elevated levels of eNOS and PAI-1.

vWF, tPA and hsCRP. While our study is limited by the sample sizes of each individual cohort of patients and the subsequent ability to power our study, we have at least revealed a trend that may be possible for further exploration in these biomarkers of indicative of endothelial cell dysfunction. This dysfunction then leads to vascular compromise that alters flow patterns and tissue perfusion which can then manifest as macroscopic system activation such as sympathetic nervous system overactivation as well as activation of the RAAS system. In addition, endothelial cell dysfunction is the first step in the generation of atherosclerosis,<sup>25</sup> and therefore higher levels of these biomarkers may serve as a proxy for an increased susceptibility to atherosclerotic plaque buildup.

Interestingly, our study also revealed a trend of higher amounts of D-dimer, nitrotyrosine, vWF, and tPA in patients with ESRD and concomitant PAD. While PAD is understood to be a disease of systemic atherosclerosis that compromises vascular flow,<sup>25</sup> less is known about how these chronic changes compare with patients who have similar changes in cardiorenal syndrome. However, our preliminary results reveal that both patients with PAD and CVD as their concomitant disorder, have a higher state of inflammation, oxidative stress, and endothelial cell dysfunction. This possibly suggests that a similar systemic disorder is occurring in both CVD and PAD in a patient with ESRD. However, as mentioned earlier the authors of this paper theorize that while the end result is similar, the mechanisms are on opposite ends of the spectrum. PAD is predominantly a disease of the arterial system and therefore the hemodynamic alterations as well as inflammatory changes that occur in the disease process result in compromised blood supply to the kidneys. This seems to therefore manifest as a “supply” issue as opposed to a “return” issue which more closely aligns with the venous congestion seen in cardiorenal syndrome. Further exploration is necessary to better understand the similarities in the microenvironments of these conditions as well as macroenvironment in these conditions. Most notably, an understanding of how systemic vascular resistance affects glomerular perfusion would be helpful to reconcile a similarity between PAD and CRS. CRS experiences a low effective circulative volume due to compromised cardiac output, thus, there is an increase in systemic vascular resistance;<sup>26</sup> similarly, patients with PAD also have an increased systemic vascular resistance due to alterations in the characteristics of the arterial wall.<sup>6</sup> Therefore, an increased systemic vascular resistance is a shared feature of CRS and arterial-renal syndrome and may manifest in a similar way when looking at the effects it has on kidney function.

When approaching patients who have cardiorenal syndrome or arterial-renal syndrome, it is important to translate these basic science findings into decisions made clinically. It is important to understand that both cohorts of patients in both disease spectrums show elevated levels of inflammatory biomarkers which serves as evidence that the vasculature in these patients are well compromised. Thus, treatment modalities that act on vessel receptors, through mechanisms involving the blood stream, or rely on fluid shifts in the body may need adjustments relative to a regular patient population. A firm understanding of

these principles incorporated with a individual's patient history ultimately creates a tailored spectrum of care that will provide a maximal possible outcome for a patient.

## Conclusion

CVD and PAD are frequently encountered in patients with ESRD. Both of these conditions were found to have elevated levels of inflammatory biomarkers reflecting the increased inflammatory state, increased amount of oxidative stress, and increasing amounts of endothelial cell dysfunction. While many of these results did not meet statistical significance, this could be an artifact due to the limited sample size of the study and inadequate power. However, our preliminary data suggests a similar process that is occurring in cardiorenal syndrome in patients with concomitant PAD and ESRD, namely, arterial-renal syndrome.


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## Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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