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Chronic Kidney Disease and its impact on cardiovascular disease and treatment modalities

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Abstract:

Kidney dysfunction is one of the most important comorbidities in heart failure. The reduced estimated glomerular filtration rate is a strong predictor of cardiovascular mortality and its associated complications. Chronic Kidney Disease (CKD) is characterized by progressive loss of kidney function, leading to either dialysis or Renal Replacement Therapy (RRT), and is associated with high mortality. The quality of life for patients with dialysis or on RRT is very poor. The primary causes of CKD are diabetes and hypertension. On the other hand, studies show that kidney diseases over time promote profound cardiovascular changes resulting in cardiovascular disease (CVD). Factors that are released from the kidney to cause cardiac phenotype changes are not well understood. The secretory proteins that play a critical role in CKD and how they mediate the progression of CVDs need further attention. In this article we review recent findings of CKD-mediated cardiovascular changes culminating in CVD and its treatment modalities.

Keywords: *Chronic kidney disease; Cardiovascular disease; Cardiorenal syndrome*

Chronic kidney disease and risk of cardiovascular disease

Kidney and heart function are closely interconnected physiologically and patho-physiologically, both in healthy and in the diseased state. Kidney function, as reflected by serum creatinine and more precisely the Albumin to Creatinine Ratio (ACR) and the estimated glomerular filtration rate (eGFR), is persistently one of the best predictors of cardiovascular outcomes in many populations [1-3]. This includes high-risk patients with congestive heart failure, post-myocardial infarctions, and those with diabetes mellitus.

In a clinical trial including patients with post-myocardial infarction receiving state of the art therapy with median lower eGFR had a 50% increased risk of cardiovascular events such as death compared with those with eGFR above the median [4]. A meta-analysis of studies assessing the relationship between heart failure and kidney dysfunction found that at least 63% of patients had mild kidney injury, and 20% had moderate or severe renal dysfunction [5]. Further, a consistent risk relationship of a 7% increase in mortality for every 10 ml/min decrease in eGFR was found. These findings were also confirmed in a larger cohort of patients with heart cessation [6]. Twenty-five percent of patients hospitalized for acute heart failure had significantly higher kidney dysfunction (eGFR less than 60 ml/min/1.73 m2). The use of diuretics may be one of the risk factors for kidney dysfunction at least in the initial phase of hospitalization for patients with heart failure [7, 8].

Patients with higher kidney dysfunction are associated with extended hospitalizations days, as well as a higher risk of short- and long-term cardiac failure. In the large-scale Acute Decompensated Heart Failure National Registry (ADHERE) consisting of 105,388 hospitalized visits of patients with acute decompensated heart failure in the United States of America, the best predictors of the outcome included both serum Blood Urea Nitrogen (BUN) and creatinine [9]. This refers to the strong independent pre- and post-kidney function of the prognostic equivalence.

Data from an Ontario heart failure population derivation cohort in the Enhanced Feedback for Effective Cardiac Treatment (EFFECT) study identified that older age, low systolic blood pressure, high serum BUN, and low serum sodium were independent forecasters of outcome [10]. In addition, a recent study of patients with diastolic heart failure showed that kidney dysfunction is associated with heart failure [11, 12], where major predictors included kidney dysfunction, age, plasma sodium,

anemia, and dementia. Thus, the presence of kidney dysfunction contributed at least 20% to the increase of heart failure-related mortality [13].

Various cross-sectional studies have shown that the Framingham risk equation is insufficient to predict the extent of CVD risk in subjects with CKD [14-16]. The non-traditional risk factors such as physical inactivity, body weight, and composition are not included in Framingham risk equations which may play an important role in promoting ischemic heart disease in subjects with CKD. Traditional risk factors such as hypertension, diabetes, dyslipidemia, smoking, and family history of premature heart disease may have a different risk relationship with cardiovascular disease in CKD as compared to the general population.

Community-based differences in Acute Kidney Injury (AKI) and CKD have been studied and African Americans are found at higher risk of kidney failure [17, 18]. The black population shows a 16% higher eGFR compared with the non-black population in age and creatinine-matched study [19]. Due to this difference removing the race coefficient is suggested but this may also cause an underestimation of eGFR in the black population, with potential unintended consequences at the individual and population levels [20]. The reason for these differences is not fully understood and thus use of race in eGFR calculations has been limited [21]. There are significant ongoing efforts to address the eGFR calculations to predict the risk of kidney failure and to better understand the racial differences.

Diabetic kidney disease and cardiovascular disease

The early marker for diabetic kidney disease is microalbuminuria which is a predictive risk marker for CKD. Microalbuminuria also causes poor glucose control, dyslipidemia, and increased blood pressure compared with diabetic subjects without microalbuminuria [22, 23].

Cross-sectional studies show for type 2 diabetic patients a stronger association between microalbuminuria and CVD as well as surrogate measures, such as carotid intima-media thickness [24]. In addition, Left Ventricular Hypertrophy (LVH) [25, 26], as well as different clinical symptoms of CVD such as peripheral vascular disease [27] and coronary artery disease [26, 28] were associated with microalbuminuria. This correlation was found in both patients with type 1 and type 2 diabetes. Likewise, longitudinal studies demonstrated that an increase in microalbuminuria leads to worse CVD outcomes and all-cause mortality in diabetic patients [26, 29-33].

Dialysis and cardiovascular disease

CVD mediated mortality is up to 30 times higher in dialysis patients as compared to the general population [34]. After stratification for age, CVD mediated death remains 5-fold higher in dialysis patients than in the general population, even in the aged population [35-37]. Moreover, kidney dysfunction contributes to the pathophysiology of a cardiorenal syndrome, including anemia, uremic cardiomyopathy, fluid overload, and secondary hyperparathyroidism. However, the unique physiology of cardiovascular abnormalities in dialysis patients remains poorly understood. Altered lipid metabolism and accumulation of gut microbiota-derived uremic toxins like trimethylamine N-oxidase (TMAO), also affect the cardiovascular function following kidney failure [38].

Because of the low levels of erythropoietin in end-stage renal disease, patients undergoing dialysis become anemic which increases the risk of cardiovascular disease [39]. Anemia promotes ischemia in the heart due to a decrease in oxygen delivery which represents a classical risk factor for atherosclerosis [40-42]. A decrease in shear stress due to changes in the signaling mechanisms in the endothelium may also contribute to vascular injury [43].

Thickening of blood vessels in patients undergoing dialysis is caused by disturbed homeostasis in vitamin D, calcium, and phosphate levels as well as fibroblast growth factor 23 [44], and chronic myocardial ischemia is caused by underlying calcification and atherosclerotic changes in the cardiac vasculature [45]. Moreover, artificial tubing and dialyzer membranes cause platelet abnormalities, and dialysis itself promotes inflammation and thrombosis [46]. Previously used complement-activating cellulose filters in hemodialysis increased the risk for anaphylactoid reactions, which is today largely prevented, as significant advancements in dialyzer membrane technology have happened since the use of Wilhelm Kolff's sausage casings started [47].

Sudden cardiac deaths are very common in patients undergoing dialysis and one of the factors/reasons for this may be the electrolyte imbalance [48]. Moreover, in each dialysis session, about 10-12 grams of amino acids are lost through the filter [49]. Prevention of malnutrition enhances the quality of life and extends the life span of dialysis patients [50]. Thus, there is a need for enhancement of the quality of life by early diagnosis and treatment of CKD patients undergoing dialysis [50]. Higher CVD-related mortality has been associated with patients undergoing peritoneal dialysis as compared to hemodialysis patients [51, 52].

Cardiovascular disease in kidney transplant recipients

As much as 50% of all-cause mortality in kidney transplant recipients is due to CVD [53-55]. The rate of CVD-mediated mortality is two times higher in transplant recipients as compared to the general population [34, 55]. Kidney transplant recipients have a lower risk for cardiovascular disease than patients on dialysis which may be related to both selection bias for those undergoing transplantation and the removal of hemodynamic and uremic abnormalities associated with dialysis in those transplant

recipients. Also, age and sex-matched data show that CVD morbidity is higher in kidney transplant recipients than in the general population. The prevalence of left ventricle hypertrophy is up to 70% [56-58], and the incidence of CVD is at least 3 to 5 times higher in patients with kidney transplants as compared to non-transplanted patients, Additionally, the prevalence of coronary artery disease was increased by 15% in patients with kidney transplants as compared to the general population [34, 59].

Cardiovascular disease in nondiabetic kidney disease

Genetic considerations:

Irrespective of the pathophysiological mechanism of the underlying genetic disease, the overall risk for CVD is increased as compared to the general population. A registry of a cohort of 116 patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD) with a mean age of 41 years had a 41% prevalence of left ventricular hypertrophy, and 23% subjects had it without hypertension, using echocardiographic methods [60]. In a study of 31 ADPKD patients with hypertension, ADPKD patients had significantly greater left ventricle myocardial infarction. Intriguingly, right ventricular function, as assessed by the myocardial performance index, was significantly higher in both ADPKD patients and normotensive patients [61], and in ADPKD patients with well-preserved renal function.

Focal segmental glomerular sclerosis is the most common glomerular disease in children and adults leading to end-stage kidney disease and ultimately renal replacement therapy [62]. There is a multifactorial reason for mortality including inflammatory and immunological mechanisms in this disease, with mutations in the APOL1 gene which is associated with a higher risk of the disease and leads to increased CVD [63-66]. High-risk mutation known as G1 and G2 in the APOL1 gene is associated with the African American population. A recent study suggested that African American individuals, having the high-risk APOL1 variant gene show a steeper decline in renal function than individuals having low-risk variants [67]. Interestingly, G1 and G2 mutations of APOL1 seem to cause cellular injury specifically in podocytes [68, 69].

Reduced estimated glomerular filtration rate (eGFR)

Reduced eGFR is associated with a high prevalence of CVD risk factors and a higher prevalence of CVD surrogates and clinical CVD. For example, several studies across a broad spectrum of populations, such as the Framingham and Framingham Offspring Studies, the Atherosclerosis Risk In Communities (ARIC) Study, the Hypertension Optimal Treatment (HOT) Study, the HOPE study, and the Cardiovascular Health Study (CHS) have shown that levels of systolic blood pressure and total cholesterol and the percentage of subjects with low HDL cholesterol are greater in patients with decreased eGFR. In addition, the percentages of patients with diabetes, ischemic heart disease, and heart failure are higher in those with lower eGFR [70-72]. Recent studies have shown that kidney function is associated with the extent of angiographic coronary disease [73, 74].

Proteinuria

Non-diabetic subjects with microalbuminuria have a higher risk of CVD as compared to diabetic patients without microalbuminuria due to high blood pressure, and dyslipidemia [75-77]. Microalbuminuria is also related to the increased thickness of the intima and media of the carotid artery in patients with hypertension [78], and electrocardiographically signs of ischemia of the myocardium [79]. Clinical CVD has been found to be increased in patients with microalbuminuria as compared to patients without microalbuminuria [77].

Longitudinal studies demonstrated that proteinuric non-diabetic kidney disease patients have an increased risk of CVD as compared to proteinuric patients with diabetic kidney disease [29, 80-87]. Microalbuminuria in nondiabetic subjects in the HOPE study was associated with a 61% increased risk of the composite endpoint of stroke, myocardial infarction, or CVD death and a 2-fold increase in risk for all-cause mortality [29]. Microalbuminuria in nondiabetic patients may reflect generalized endothelial dysfunction [88-91] or abnormalities of the fibrinolytic and coagulation pathway, which may be a marker of the underlying inflammatory status [92] or may denote the greater severity of the target end-organ damage as opposed to diabetic patients.

Risk factors and pathophysiology for a Cardiorenal Syndrome (CRS)

The common primary cause for kidney dysfunction in the setting of heart failure or cardiac dysfunction is diabetes, hypertension, and underlying vascular diseases [93].

In general, older patients with a history of either heart failure, kidney failure, or both have higher mortality. The risk factors for diuretic resistance or kidney dysfunction in the setting of acute decompensated heart failure are not well described, but likely are also dominated by a similar risk factor.

The pathophysiology of a CRS likely varies according to the specific clinical conditions. Studies suggest that intra- and inter-renal hemodynamics such as systemic [94] and trans-renal perfusion pressure [95] including neurohormonal factors [96] are closely associated with a CRS. Likewise, an elevated central venous pressure was associated with an increased risk of mortality and AKI in critically ill adult patients hospitalized in the intensive care unit [97]. Therefore, reducing the central venous pressure can result in a significant enhancement in the blood flow of the kidney and ultimately increase the urine output.

Patients with diabetes and hypertension have a significant reduction in glomerular filtration, which further worsens any pre-existing kidney dysfunction. Activation of arterial baroreceptors and intra-renal sensors mediates the activation of neurohormonal factors. This activates intrinsic self-defence mechanisms to maintain blood pressure, and together with the intravascular volume that also activates the renin-angiotensin system, which was defined as the sympathoadrenal system. All these factors cause vasoconstriction in the kidney leading to decreased renal flow and low GFR. Subsequently, inflammatory cytokines are released because of hypoxia which leads finally to kidney dysfunction.

Recent reports indicate that the presence of a low-flow state does not explain the pathophysiology of CRS completely. The Acute Decompensated Heart Failure National Registry (ADHERE) showed that increased serum creatinine levels were similar among patients with acute heart failure and a reduced versus preserved systolic function [57]. Additionally, patients with evidence of acute CRS have preserved or elevated blood pressure and normal left ventricular ejection fraction [98]. Reduction in renal blood flow in patients with decompensated heart failure with relative preservation of their glomerular filtration rate was found [14]. The decrease in glomerular pressures and reduced GFR were driven by pre-glomerular vasoconstriction from extreme levels of RAAS and neurohormonal activation [99].

In this context adenosine is a factor that is related to the tubuloglomerular response. It is released by the kidney under stress and binds on the receptors of the afferent arterioles and causes vasoconstriction, which decreases blood flow in the kidney [100]. This pathway needs further attention to better understand the effects of blocking adenosine and its outcome on the resulting kidney function.

Clinical challenges in the management of patients with cardiorenal syndrome

Clinicians are facing increasing challenges in the treatment of patients with contradicting medication available for the two individual organs heart and kidney. For the kidney, it is important to regain its function by increasing the vascular volume by increasing the overall sodium load while salt on the other side will worsen the cardiac complications. In contrast, cardiologists treating a patient's volume overload and cardiac congestion with aggressive use of diuretics will lead to a decrease in blood pressure which can cause acute kidney dysfunction. Not surprisingly, many patients end up being discharged from the hospital either still volume loaded or markedly worse in terms of renal function. Consequently, there is a high readmission rate for patients recently discharged from hospitals with heart failure or renal failure. Thus, separately nephrologists and cardiologists will often provide counsels that may be incompatible and thus need to know the underlying CVD and CKD, respectively.

Schematic of cross-talk between cardiac complications and kidney disease are shown in (Figure 1).

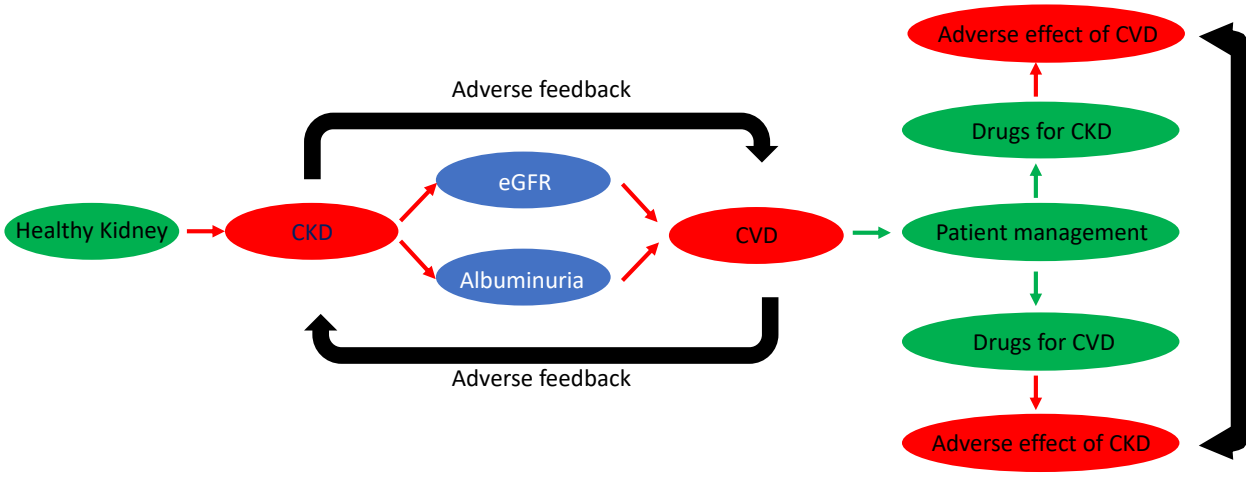

Figure 1: Progression of chronic kidney disease leads to decrease in eGFR and increase in albuminuria. Decreased eGFR and increased albuminuria possess higher risk of cardiovascular disease.

Common strategies for treating the cardiorenal syndrome

Moving forward, the identification of CRS is important and long-term treatment plans should be given priority. There is a need for an optimized therapy that can preserve kidney function as well as heart function. Novel adenosine receptor blockers and other improved volume regulators that can preserve both kidney and cardiac function are much awaited to be developed.

The newer class of drugs targeting multiple symptoms

In recent years, inhibitors of Sodium-Glucose Co-Transporter 2 (SGLT2), Glucagon-Like Peptide-1 receptor (GLP1), and Dipeptidyl Peptidase IV (DPP4) inhibitors have been approved for patients with diabetes for glycemic control.

SGLT2 Inhibitors: SGLT2 inhibitors decrease the risk of heart

failure, hospitalizations, and serious kidney outcomes among patients with diabetes [101-103]. The cardio-renal benefits are so dramatic that they cannot be explained by the glucose-lowering action of SGLT2 inhibitors [104]. Hence, it is suggested that heart and kidney protection by SGLT2 inhibitors would be apparent in patients without diabetes as well [105, 106]. SGLT2 inhibition in patients with type 2 diabetes improved glomerular hemodynamic function, along with the reduced risk of CKD and CVD [107].

GLP1 Inhibitors: The major pathways underlying the GLP-1 mechanism of action in the kidney are regulation of atrial natriuretic peptide and effects on the renin-angiotensin system. In Dahl salt-sensitive rats, infusion of GLP-1 increased the eGFR, urinary flow, and urinary sodium. GLP-1 decreases reactive oxygen species (ROS) production and inflammation in vivo and in vitro by increasing the GLP-1 receptor [108]. GLP-1 receptor agonists (RAs) increase insulin secretion and stimulate glucose uptake, leading to a reduction in glycated hemoglobin (HbA1c) [109]. In randomized controlled trials, GLP-1 RAs reduce systolic blood pressure by 1 to 2 mm Hg, with lesser effects on diastolic blood pressure [110]. In addition, GLP-1 RAs did not reduce the incidence of new-onset of hypertension [62] and further increased heart rate by 2 to 3 beats per minute [110]. In a trial with healthy obese men with exenatide administration, there was a 33% reduction in afferent arteriolar resistance and no change in efferent arteriolar resistance a single dose, thus increasing the blood flow and eGFR [111]. In addition, GLP-1 RAs reduce cardiovascular (CV) risk compared to placebo in cardiovascular outcome trials (CVOTs). GLP-1 RAs have only a modest effect on the risk of heart failure after hospitalization [112].

DPP4 Inhibitors: DPP-4 inhibitors show protection from fibrosis, reduction in albuminuria, and inhibit the progression to advanced CKD. DPP4 inhibitor, linagliptin, decreases the expression of the advanced glycation end product (AGE) receptor which in turn lowers the oxidative stress and inflammation in mouse models. Thus, linagliptin leads to decreased progression of advanced Diabetic Kidney Disease (DKD).

Although, multiple animal models show beneficial effects of linagliptin on kidney fibrosis, its translation into the patients with DKD to inhibit its progression is not affirmative. However, DPP-4 inhibitors offer good glycemic control in patients with DKD, and hypertension [113]. Saxagliptin, another DPP4 inhibitor in an assessment of vascular outcomes recorded in patients with diabetes thrombolysis in myocardial Infarction trial, showed an association with significant reductions in albuminuria [114]. However, a 2-year follow-up cohort did not show any difference in eGFR or the incidence of kidney endpoints, such as doubling of the serum creatinine values or kidney failure [113]. Similarly, sitagliptin, there was a significant improvement in albuminuria but no change in eGFR [115].

The primary result of the cardiovascular and renal microvascular outcome trial with linagliptin was a cardiovascular disease composite, including nonfatal myocardial infarction, cardiovascular death, and nonfatal stroke. Linagliptin trial showed a cardiovascular safety profile with no significant difference in kidney outcomes with a 40% decrease in eGFR [116]. Notably, patients randomized to receive linagliptin had less progression of albuminuria [36]. Thus, additional trials with longer follow-up times are warranted to be conducted to assess its effect on the progression of DKD.

Summary of the effects of DPP-4, GLP-1, and SGLT-2 inhibitors in cardiovascular disease, diabetic and diabetic kidney disease has been shown in (Figure 2).

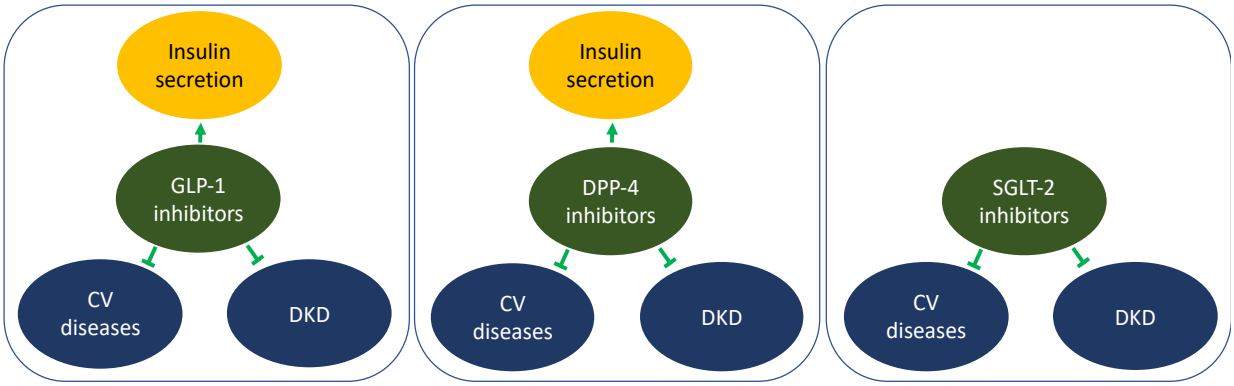

Figure 2: GLP-1 and DPP-4 and SGLT-2 inhibitors offers protection in cardiovascular and diabetic kidney disease. In addition, GLP-1 and DPP-4 inhibitors offers additional benefit for management of diabetes by improving insulin secretion.

Open Questions

There are many remaining questions such as the effect of a low range decrease in eGFR on the development of CVD (89 to 60), and for instance if non-traditional risk factors and CKD at all stages is a risk factors for CVD. Also, how cellular remodeling of the left ventricle happens in patients with CKD. All of this should be further addressed to improve treatment strategies at an early stage of disease in affected patients.

Conflict of Interest

Authors declare no conflict of interests.

Authors Contributions

AKA conceptualized the manuscript, searched for the literature, and wrote the manuscript. LZ searched the literature and edited the manuscript. AW and LLH edited the manuscript. All the authors approved the manuscript.

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