Cardiovascular Disease in Patients with Chronic Kidney Disease

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Abstract

Kidney and cardiovascular diseases are strongly associated due to the connections between the heart and the kidneys; kidney disease may even be seen as a cardiovascular risk. The Chronic Kidney Disease (CKD) Prognosis Consortium showed that CKD severity was related to cardiovascular death risk, among other factors. When reduced estimated glomerular filtration rate and albuminuria – both biomarkers for declining renal function – are present in a patient, the rate of cardiovascular events increases significantly. Kidney and heart diseases are linked with regard to coronary atherosclerosis, myocardial disease, valvular calcification, and atrial and ventricular arrhythmias. CKD and end-stage renal disease (ESRD) patients with coronary atherosclerosis frequently have accentuated calcification; many CKD-related factors accelerate the calcification process. These may include traditional risk factors such as hypertension or diabetes, as well as non-traditional risk factors such as uremia, anemia, and increased coagulation proteins. This is also associated with more stable lesions, often leading to episodes of silent and symptomatic coronary ischemia in these patients. CKD is linked to heart failure by accentuating pressure overload, volume overload, and cardiomyopathy, the three major pathophysiologic mechanisms causing left ventricle failure. Hemodialysis itself may lead to myocardial disease through “myocardial stunning,” in which episodes of hypotension during hemodialysis cause transient wall motion abnormalities, worsening survival overtime. Short daily hemodialysis in the home setting may be associated with improved outcomes. CKD and ESRD patients often experience accelerated aortic valvular and mitral annular calcification and fibrosis. These patients should receive echocardiography during care, to evaluate for valve disease severity as well as the left ventricular systolic and diastolic function. Finally, CKD patients have many of the myocardial and hemodynamic factors of arrhythmia. 62% of cardiac deaths in the United States Renal Data System database are due to arrhythmias. CKD and ESRD patients should receive individualized treatment and frequent monitoring due to the increased risk of adverse events and iatrogenic death in this patient population. One option is to form hybrid “cardionephrology” teams comprised cardiologists and nephrologists. This will optimize care for cardiorenal patients and boost interest in the nephrology field, which is presently lagging.

Key words: Chronic kidney disease, atherosclerosis, heart failure, aortic valve, mitral valve, arrhythmia, sudden death

Introduction

The heart and the kidneys are inextricably linked through vascular, neurological, hormonal, and cellular signaling systems. The kidneys are the most vascular organ in the body, receiving a quarter of cardiac output at rest. Thus, kidney disease is strongly associated with cardiovascular illness and, in fact, may be considered as a cardiovascular risk state. In addition, when either organ sustains injury or begins to fail, there appears to be a consequential effect on the other organs in either an adaptive or maladaptive response that we now recognize as a “cardiorenal syndrome(s).” This chapter will review the connections between the heart and the kidneys from epidemiological, biological, and clinical perspectives with the aim of gaining greater appreciation for this important interface in both acute and chronic care.
Why Does Ckd Convey Increased Cardiovascular Risk?

The CKD Prognosis Consortium (CKD-PC) was established in 2009 by the Kidney Disease: Improving Global Outcomes (KDIGO) organization in an attempt to understand the risks of declining renal filtration function represented by the estimated glomerular filtration rate (eGFR) and the presence of albumin in the urine indexed to the filtered creatinine concentration (urine albumin: creatinine ratio [ACR]). In a series of manuscripts, this group used a very large, pooled database (1,555,332 subjects in 45 cohorts) to demonstrate that the severity of CKD was related to the risks of all-cause mortality, cardiovascular death, acute kidney injury, progressive CKD, and end-stage renal disease (ESRD) as shown in Figure 1. These relationships can also be shown in a “heat map” of risk as demonstrated in Figure 2. It is important to understand that when both eGFR and elevated ACR overlap, there appears to be magnified risk for all outcomes. Data from the National Kidney Foundation Kidney Early Evaluation Program (KEEP) and the National Health and Nutrition Examination Survey suggest that the majority of individuals with CKD in the younger age groups are identified by albuminuria while those in the older age strata have reduced eGFR (<60 ml/min/1.73 m²) as the CKD marker [Figure 3]. Importantly, the overlap between the two markers is less common than one alone in these large populations. However, when both reduced eGFR and albuminuria are present in the same patient, the predicted and observed rates of cardiovascular events are markedly increased over a relatively short (<5 years) duration. Thus, it is critical that in every patient, the eGFR is calculated from the patient’s age, gender, race, and serum creatinine using standardized equations and the urine ACR is checked on a first morning voided specimen. Structural kidney disease (including polycystic kidney disease) detected by imaging studies is also characterized as CKD in the absence of eGFR and ACR abnormalities. The CKD-PC was limited in terms of non-fatal cardiovascular outcomes; therefore, we must turn our attention to other sources of information to understand the connections to coronary atherosclerosis, myocardial disease, valvular disease, and arrhythmias.

The term “reverse epidemiology” has been applied to patients with ESRD for many risk factors, particularly body weight. This means that in the general population, increased adiposity, as expressed with the body mass index, is consistently associated with cardiovascular events and reduced survival. However, in ESRD, increased BMI confers improved survival. This suggests that increased adiposity is the inverse of cachexia. That is, as chronic disease progresses, cachexia and reduction in weight are common observations on the pathway towards death. Thus, retention of adiposity is associated with survival. Reverse epidemiology has also been observed with total cholesterol and albumin which are proxies for nutritional intake which again is inversely related to the degree of cachexia.

Kidney Disease and Coronary Atherosclerotic Calcification

Data from many studies suggest that the CKD milieu promotes the early initiation and accelerated course of coronary atherosclerosis. Since CKD is strongly associated with traditional coronary risk factors including hypertension,
diabetes, dyslipidemia, and smoking, the combination of these factors may be reflected by CKD, and thus, its relationship is amplified by positive confounding. However, when adjusting for these factors, CKD has been consistently associated with non-fatal myocardial infarction and cardiovascular death. A prominent feature of coronary atherosclerosis in patients with CKD and ESRD is accentuated calcification which occurs in all cases of atherosclerosis when reviewed at necropsy. Initially, calcium deposits on cholesterol crystals in the subendothelial space. However, the progression of atherosclerosis involves a multitude of local and systemic factors which stimulate vascular smooth muscle cells to undergo osteoblastic transformation into

Figure 2: Adjusted risk of outcomes according to eGFR and urine ACR. Adapted from reference.

Figure 3: Identification of CKD by eGFR and urine ACR in KEEP, N = 40,013 and NHANES, N = 10,486. Adapted from reference.
osteocyte-like cells which deposit calcium hydroxyapatite crystals into both the subendothelial and medial compartments of blood vessels. Many factors have been implicated in CKD to accelerate this process including low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, vascular calcification factor, osteoprotegerin, and most notably phosphorus. As eGFR falls, there is retention of phosphate which can stimulate the Pit-1 receptor on vascular smooth muscle cells, thereby facilitating the osteoblastic transformation. Of note, neither dietary calcium nor the plasma concentration of calcium has been independently associated with calcific deposits in the coronary arteries. As CKD progresses, coronary artery disease is commonly identified on a variety of clinical studies, frequently as longer lesions and in more proximal vessels. Fortunately, more extensive calcification – while related to the burden of coronary disease – is also associated with more stable lesions; thus, CKD patients often have stable but extensive CAD leading to episodes of both silent and symptomatic coronary ischemia.

It has been suggested that there are both traditional and non-traditional risk factors that may contribute to more accelerated atherosclerosis in persons with CKD. The traditional risk factors include elevated LDL-C, hypertension, diabetes mellitus, smoking, and family history of premature coronary disease (first-degree relative female before age 55 and male before age 45 years). Non-traditional risk factors in CKD have been variously mentioned in literature and include blood markers of mineral and bone disorder (hyperphosphatemia, elevated calcium-phosphorus product, osteopontin, and hyperparathyroidism), C-reactive protein, uremia, asymmetric dimethylarginine and reduced nitric oxide availability, anemia, increased unbound iron (catalytic or poorly liganded iron), homocysteine, fibrinogen, and increased coagulation proteins. None of these factors have been sufficiently tested in prospective studies to be considered a therapeutic target for prevention in CKD patients with atherosclerosis.

Heart Failure in Ckd

CKD promotes the three major pathophysiologic mechanisms by which the left ventricle can fail: Pressure overload, volume overload, and cardiomyopathy. Since hypertension is both a determinant and a consequent of CKD, the vast majority of CKD patients have longstanding histories of elevated blood pressure and increased cardiac afterload resulting in left ventricular hypertrophy and increased left ventricular mass. Salt and water retention result in chronic volume overload. Nephrotic syndrome and loss of oncotic forces result in worsened fluid retention and edema. Uremia and retention of many substances (indoxyl sulfate and p-cresol) result in impaired myocyte function in both systole and diastole. It has become recently understood that the production of fibroblast growth factor-23 from bone in response to CKD phosphate retention has off-target effects on the left ventricular myocardium, resulting in increased left ventricular mass and cardiac fibrosis.

Figure 4: Pathophysiology of cardiorenal syndrome type 1. ADHF = acutely decompensated heart failure. AKI = acute kidney injury. Reproduced with permission from reference.
myocardial tissue has a reduced capillary density compared to that of persons with normal renal function. Considerable evidence is accumulating that “CKD cardiomyopathy” is manifest by impaired systole and diastole with biomarker and imaging evidence of cardiac fibrosis. The observation that galectin-3 levels correlate with type III aminoterminal propeptide of procollagen, matrix metalloproteinase-2, and tissue inhibitor of metalloproteinase-1 suggests that myocardial macrophage infiltration enhances turnover of extracellular matrix proteins in patients with CKD.\(^9\) Thus, patients with CKD are at very high risk for the development of heart failure associated with markedly impaired cardiorespiratory function and the cardinal features of fatigue, effort intolerance, edema, and clinical findings including pulmonary congestion and elevation of B-type natriuretic peptides (BNP and NT-proBNP).\(^{10}\) When acutely decompensated heart failure is present, then a vicious cycle of worsened renal filtration function, venous and renal congestion, and further retention of salt and water can occur. This is commonly termed cardiorenal syndrome type 1 [Figure 4].\(^{11}\)

It has become increasingly recognized that hemodialysis itself may contribute to myocardial disease through the process of “myocardial stunning,” in which there are transient wall motion abnormalities that are related to episodes of hypotension during hemodialysis. The greater the number of segmental wall motion abnormalities, the worse the survival overtime [Figure 5]. Recent analyses suggest that short daily hemodialysis in the home setting is associated with fewer episodes of intradialytic hypotension, regression of left ventricular hypertrophy, and a 41\% lower risk of heart failure, fluid overload, and cardiomyopathy.\(^{12}\)

**Valvular Calcification**

Accelerated aortic valvular and mitral annular calcification and fibrosis are common in patients with CKD and nearly universally present in patients with ESRD. The murmur of aortic valve sclerosis is found in the majority of patients while the mitral annular disease is usually silent and detected only by echocardiography or other forms of imaging. The aortic valve sclerosis and calcification can progress to symptomatic aortic stenosis while the mitral annular disease can result in very mild functional stenoses or regurgitation by Doppler but rarely requires surgical attention. Both valvular lesions can be the substrate for acute infective endocarditis in ESRD patients with temporary dialysis catheters, which occurs at the rate of 6–8\% per year. *Staphylococcus aureus* is the main cause (75\%) of vascular access-related bacteremia among patients receiving long-term hemodialysis. When endocarditis occurs in this setting, the operative mortality rate can be in excess of 50\%.\(^{13}\) Most patients with CKD should undergo echocardiography at some point in their care not only to evaluate for the extent of valve disease but also to assess the left ventricular systolic and diastolic function.

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**Figure 5:** Pathophysiologic rationale for myocardial stunning in ESRD on hemodialysis

**Figure 6:** Major adverse renal and cardiac events (MARCE) are strongly associated with AKI and raise the possibility of strategies that reduce AKI, translating into improved clinical outcomes as measured by the time to first MARCE event in clinical trials. Reproduced with permission from reference\(^{18}\)
Atrial and Ventricular Arrhythmias

Patients with CKD have the myocardial and hemodynamic determinants of all forms of arrhythmias. In the United States Renal Data System database, 62% of cardiac deaths (27% of all deaths) are attributable to lethal arrhythmias.[14] Atrial fibrillation occurs at an elevated rate in patients with CKD and is associated with an increased risk of cardioembolic stroke compared to those with normal renal function at all levels of the CHA₂DS₂-VASc score. Recent data are supportive of apixaban (either 2.5 mg or 5 mg p. o. bid) potentially in place of warfarin for CKD patients with non-valvar atrial fibrillation at high risk of stroke or systemic embolism.[15] Due to accelerated myocardial fibrosis and the presences of both macrovascular and microvascular disease, reentrant ventricular tachycardia is believed to be the prelude to ventricular fibrillation followed by asystole and sudden death. Increased premature atrial and ventricular beats, when seen on monitoring, can be harbingers of atrial fibrillation and ventricular tachycardia, respectively. Electrolyte shifts – particularly changes in potassium concentration that occurs in CKD and are accentuated with forms of dialysis – are also believed to play a role in ventricular arrhythmias and sudden death, most likely due to ventricular fibrillation. The role of implantable cardio-defibrillators is controversial at the time of this writing, given the associated shortened survival and the risks of device and lead infection in ESRD.[16] Each guidelines-based approach in the population of patients with heart disease and normal renal function is complicated by increased adverse events and even iatrogenic death in patients with CKD and ESRD. Thus, therapy must be individualized and very frequent monitoring is required.

Cardionephrology Collaboration

In light of the strong link between kidney disease and heart disease, there is a great need for collaboration between cardiologists and nephrologists. This is becoming increasingly relevant with the growing use of mechanical devices such as left ventricular assist devices and novel cardiorenal therapies.[17] Rangaswami et al. advocated the formation of hybrid “cardionephrology” teams to controvertial the time of this writing, given the associated shortened survival and the risks of device and lead infection in ESRD.[16] Each guidelines-based approach in the population of patients with heart disease and normal renal function is complicated by increased adverse events and even iatrogenic death in patients with CKD and ESRD. Thus, therapy must be individualized and very frequent monitoring is required.

Summary

The connection between kidney and heart disease can be viewed in four domains: Coronary atherosclerosis, myocardial disease, valvular abnormalities, and arrhythmias. CKD plays a role in the pathogenesis, presentation, outcomes, and management of each manifestation of CVD. Future research is needed to better understand the unique mechanisms at work in patients with CKD that promotes and worsens CVD outcomes. Practical strategies, such as the formation of dedicated cardionephrology teams, are needed to guide clinicians in the appropriate management of this high-risk population.

References


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