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Spectrum of cardiorenal disease

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Cardiorenal disease

The modern day, worldwide epidemics of obesity and hypertension (HTN) are central drivers of a secondary epidemic of type 2 diabetes with combined chronic kidney disease (CKD) and cardiovascular disease (CVD). Approximately half of those with diabetes will develop CKD. Conversely, half of all cases of end-stage renal disease (ESRD) are due to diabetic nephropathy. With the aging of the general population and cardiovascular care shifting towards the elderly, an understanding of why decreasing levels of renal function act as a major adverse prognostic factor after a variety of cardiac events is imperative. The heart and kidney are inextricably linked via hemodynamic and neurohumoral function (Fig. 1). Considerable evidence shows that CKD accelerates atherosclerosis, myocardial disease, valvular disease, and promotes an array of cardiac arrhythmias.


Chronic kidney disease and cardiovascular risk

Chronic kidney disease is defined through a range of estimated glomerular filtration rate (eGFR) values by the National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative (KDOQI) (Table 1). A common definition for CKD stipulates an eGFR of < 60 ml/min/1.73 m² or the presence of > 30 mg/g of albuminuria on a spot urine sample. Although with normative aging (age 20 to 80), the eGFR declines from ~130 to 60 ml/min/1.73 m², a variety of pathobiologic processes appear to begin when the eGFR drops below 60 ml/min/1.73 m². Most studies of cardiovascular outcomes have found that a breakpoint for the development of contrast nephropathy, restenosis post percutaneous coronary intervention (PCI), recurrent myocardial infarction (MI), diastolic/systolic heart failure (HF), cardiovascular and all-cause death occurs below an eGFR of 60 ml/min/1.73 m², which roughly corresponds to a serum creatinine (Cr) of > 1.5 mg/dl in the general population. Because Cr is a crude indicator of renal function, and often underestimates renal dysfunction in women and the elderly, calculated measures of eGFR or creatinine clearance (CrCl) using the Cockcroft-Gault equation or the Modification of Diet in Renal Disease (MDRD) equation are superior methods for the assessment of renal function. The four-variable MDRD equation for CrCl is the preferred method since it does not rely on body weight.

In addition, microalbuminuria at any level of eGFR is considered to represent CKD (Table 2), and has been thought to occur as the result of glomerular damage in the kidneys due to diabetes and HTN-related changes in the glomeruli. There have been several definitions proposed for microalbuminuria. The most widely accepted is a random urine albumin/creatinine ratio (ACR) of 30-300 mg/g. An ACR > 300 mg/g is usually considered gross proteinuria. There is a stepwise increase in observed rates of coronary heart disease mortality as proteinuria worsens (Fig. 2). Thus, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) has recognized CKD as an independent cardiovascular risk state (Fig. 3). This risk state has a host of vascular and metabolic abnormalities, which will be discussed below (Fig. 4).

Contrast nephropathy

The overall risk of contrast nephropathy, defined as a transient rise in Cr > 25% above the baseline or an absolute rise > 0.5 mg/dl, occurs in approximately 13% of nondiabetics
However, when they occur, they are related to catastrophic disease. Fortunately, cases of contrast nephropathy leading to dialysis are rare (0.5-2.0%) among all patients undergoing PCI and 20% of diabetics undergoing PCI. It is critical to understand that the risk of contrast nephropathy relates in a curvilinear fashion to the eGFR as it falls below 60 ml/min. Fortunately, cases of contrast nephropathy leading to dialysis are rare (0.5-2.0%) among all patients undergoing PCI. However, when they occur, they are related to catastrophic outcomes including a 36% in-hospital mortality rate and a two-year survival of only 19%. While not directly attributed to contrast nephropathy, transient rises in Cr are directly related to longer intensive care unit and hospital ward stays (3 and 4 more days, respectively) after bypass surgery. Even transient rises in Cr translate to differences in worsened adjusted long-term outcomes after PCI.

Acute coronary syndromes

Multiple studies have found that the elderly and those with diabetes have higher rates of silent ischemia. Likewise, patients with CKD have shown higher rates of silent ischemia, which cluster with serious arrhythmias and other cardiac events. Hemodialysis patients with ESRD bear considerable hemodynamic stress three times per week during dialysis sessions. Several studies have demonstrated a relationship between ST-segment depression and release of cardiac enzymes (primarily troponin T), before or during dialysis, and poor long-term survival. From a practical perspective, it is important to understand that the risk of contrast nephropathy relates in a curvilinear fashion to the eGFR as it falls below 60 ml/min.
to realize that patients with CKD presenting to the hospital with chest discomfort represent a high-risk group, having a 40% cardiac event rate at 30 days. In making the diagnosis of acute myocardial infarction (AMI) in patients with CKD or ESRD, troponin I is the preferred biomarker based on its kinetic profile in patients with renal impairment. The skeletal myopathy of renal disease can elevate creatine kinase, myoglobin, and some troponin T assays, making these tests less desirable. In addition to an elevated biomarker of cardiac injury, supporting evidence of the diagnosis of AMI could be characteristic chest pain, electrocardiographic changes (ST-segment elevation or depression, new Q-waves), or the identification of a culprit lesion on angiography. Because of the high event rate and prevalence of CVD among patients with CKD, it is advisable to consider admission to the hospital when the presenting symptom is chest discomfort and the eGFR is <60 ml/min/1.73 m² or if the patient has ESRD and is on dialysis.

Retrospective studies of coronary care unit patients have identified renal dysfunction as the most significant prognostic factor for long-term mortality when adjusting for other clinical factors including age, gender, and comorbidities. In addition, retrospective studies of patients with AMI consistently find renal dysfunction as an independent predictor of death, with a greater impact on mortality than baseline demographics or therapies received (Fig. 5). Patients with ESRD have the highest mortality after AMI of any large, chronic disease population.

Explanations for poor outcomes in patients with renal dysfunction

Four reasons may explain why patients with renal dysfunction have poor cardiovascular outcomes in a variety of settings: 1) excess comorbidities associated with CKD and ESRD, in particular diabetes and heart failure, 2) therapeutic nihilism, 3) toxicity of therapies, and 4) special biologic and pathophysiologic factors in renal dysfunction which cause worsened outcomes. In one study by Beattie and coworkers, the comorbidities of patients with ST-segment elevation myocardial infarction (STEMI) and CKD (mean Cr = 2.7 mg/dl), included: older age (mean 70.2 years), diabetes (38.1%), and prior heart failure (23.2%). Likewise, those with ESRD had similar rates of comorbidities including: age (mean 64.9 years), diabetes (40.4%), and prior heart failure (31.7%). This study found that, among the CKD and ESRD groups, there were lower rates of use of reperfusion therapy (thrombolysis or primary angioplasty) and beta-blockers, suggesting some contribution to poor outcomes from underutilization of proven therapies (therapeutic nihilism). It is possible that patients with renal dysfunction may present later in their course, have more contraindications, or have other aspects about their presentations that prompt clinicians to use fewer therapies or take a more conservative approach.

Data on the toxicity of treatments for ACS due to renal dysfunction are often unavailable, primarily because of exclusion of CKD patients from these trials. The primary defects in thrombosis attributable to uremia are excess thrombin generation and decreased platelet aggregation. Hence, CKD and ESRD patients can have increased rates of coronary thrombotic events and increased bleeding risks at the same time. In patients with renal dysfunction, the risks of bleeding elevate with aspirin, unfractionated heparin, low-molecular weight heparin, thrombolytics, glycoprotein IIb/IIIa receptor antagonists, and thienopyridine antiplatelet agents. This is primarily because uremia causes platelet dysfunction in a mechanism that is independent, and therefore, additive to pharmacologically induced platelet antagonism or anti-thrombosis. In patients with renal dysfunction, the best measure of bleeding risk is the bleeding time. Bleeding complications account for only a small part in the differences seen in mortality between CKD and ESRD and those with preserved renal function with AMI.

The final and most important reason why patients with CKD and ESRD have poor outcomes after ACS is the enhanced vascular pathobiology induced by the chronic renal failure state. The processes that contribute to accelerate atherosclerosis include a dyslipidemia characterized by decreased function of lipoprotein lipase, reductions in high-density lipoprotein cholesterol (HDL-C), elevated triglycerides, and normal LDL-C (Fig. 3). In addition, accelerated vascular calcification is due in part to hypercalcaemia, hyperphosphatemia, elevated parathyroid hormone, and is possibly worsened by chronic acidosis and mobilization of calcium from bone. Elevations in homocysteine and other thiols are present when the eGFR drops below 60 ml/min/1.73 m², enhancing oxidation of LDL-C, and progression of atherosclerotic lesions. Importantly, renal dysfunction is a highly inflammatory state, associated with higher rates of plaque rupture and incident CVD events. In addition, observed rates of restenosis are higher in patients with CKD (Fig. 6). Lastly, chronic hyperactivation of the sympathetic nervous system and an imbalance between endothelin, a powerful vasoconstrictor, and nitric oxide, a local paracrine vasodilator, may worsen HTN and may augment intravascular wall stress that could further contribute to incident CVD events.

Congestive heart failure

The diagnosis of HF with concomitant renal failure

Fig. 7. Relationship between GFR, ejection fraction, and mortality in the PRIME II study in patients with HF. Reproduced with permission from Hilleges HL, Gribbs AR, de Kam PJ, et al. Renal function, neurohormonal activation, and survival in patients with chronic heart failure. Circulation. 2006;102:263-10. RR = relative risk, GFR = glomerular filtration rate, LVEF = left ventricular ejection fraction.


Valvular heart disease

Impaired renal function has been linked to mitral annular calcification and to aortic sclerosis. Advanced thickening of the cardiac valves and calcification has been observed in patients with ESRD. Some 80% of patients with ESRD have the murmur of aortic sclerosis. Importantly, neither of these lesions usually progress to the point where studies beyond echoangiography are needed. There are no published cases of renal dysfunction being isolated as the cause of valvular disease that required surgical intervention. However, CKD may accelerate degeneration of tissue valvular prosthesis. Bacterial endocarditis may develop in those patients with ESRD who have temporary dialysis access catheters. Endocarditis with common pathogens including staphylococcus, streptococcus, and enterococcus, in the aortic or mitral position, has a mortality rate of > 50% in this setting. It becomes very difficult to treat given the continued need for dialysis access and the delay imposed by placement of permanent arteriovenous shunts or fistulas. Unfortunately, surgical mortality for valve replacement in ESRD due to endocarditis is quite high. Infection, and endocarditis in particular, is an increasingly common cause of death in patients with ESRD.

Arrhythmias

Uremia, hyperkalemia, and disorders of calcium-phosphorous balance have all been linked to higher rates of atrial and ventricular arrhythmias. Given a concurrent substrate of left ventricular hypertrophy, left ventricular dilation, HF, and valvular disease, it is not surprising that higher rates of virtually all arrhythmias have been reported in CKD, including bradyarrhythmias and heart block. Caveats for
practical management include dose adjustment for many antiarrhythmic medications including digoxin, sotalol, and procainamide. Of concern, CKD and ESRD, in particular, may cause elevated defibrillation thresholds and failure of implantable cardioverter-defibrillators (ICD's). Until this association is better understood, patients receiving ICD's should have frequent surveillance and consideration for non-invasive programmed stimulation for appropriate antitachycardia and defibrillation therapy. Given the high rates of sudden death in patients with ESRD, clinical trials of prophylactic ICD's in this population are under consideration.

Summary

Recognition has increased over the last decade that CKD patients have high risk for CVD. Frequent clinical scenarios where renal function influenced care include contrast nephropathy, ACS, HF, valvular disease, and arrhythmias. Results from retrospective studies and clinical trial subgroups form the basis of current recommendations given the lack of prospective randomized trials in CKD and ESRD. It is hoped that further study of the adverse metabolic milieu of chronic renal failure will likely lead to generalizable diagnostic and therapeutic targets in this population.

References