REVIEW

Cardiovascular Pathophysiology in Chronic Kidney Disease: Opportunities to Transition from Disease to Health

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ABSTRACT

Background: Chronic kidney disease (CKD) is common, and is associated with a high burden of cardiovascular disease. This cardiovascular risk is incompletely explained by traditional risk factors, calling attention to a need to better understand the pathways in CKD contributing to adverse cardiovascular outcomes.

Findings: Pathophysiological derangements associated with CKD, including disordered sodium, potassium, and water homeostasis, renin-angiotensin-aldosterone and sympathetic activity, anemia, bone and mineral metabolism, uremia, and toxin accumulation may contribute directly to progression of cardiovascular disease and adverse outcomes.

Conclusion: Improving cardiovascular health in patients with CKD requires improved understanding of renocardiac pathophysiology. Ultimately, the most successful strategy may be prevention of incident CKD itself.

Key Words: cardiorenal syndrome, cardiovascular disease, chronic kidney disease, renocardiac syndrome

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INTRODUCTION

Cardiovascular diseases (CVD), including hypertension, currently affect 36.9% of the US population and account for $444.2 billion in direct and indirect costs per year.[1] By 2030, costs are projected to exceed $1 trillion. These costs are untenable, and sound the call for a transition in focus from treatment of disease to promotion of health.

In no population is this more relevant than individuals with chronic kidney disease (CKD). Defined by evidence of kidney damage or reduction in glomerular filtration rate for at least 3 months, CKD affects more than 1 in 6 US adults, including more than 500,000 with end-stage disease requiring renal replacement therapy. In this population, particularly those on hemodialysis, the burden of CVD is magnified, including coronary and peripheral arterial disease, atrial fibrillation, stroke, congestive heart failure (CHF), and sudden cardiac arrest (SCA). In the context of primary CKD, such incident CVD has been referred to as type 4 cardiorenal syndrome, or chronic reno-cardiac syndrome.[2]

Although overall cardiovascular mortality in patients with CKD has declined over the past 2 decades, driven importantly by reduction in mortality related to acute myocardial infarction (MI) in parallel with global advances in reperfusion therapy, antiplatelets, and quality of care, risks for death due to CHF (5%) and SCA (26%) have remained steady.[3,4] Three factors must be considered.

First, poor outcomes reflect the difficulty of treating CVD in CKD. Data to inform optimal therapy are limited, due to systematic exclusion of patients with advanced CKD from many seminal trials. Flexibility to diagnose and treat disease is reduced as a result of limitations on use of standard tools of care, such as iodinated contrast dye and gadolinium, renin-angiotensin-aldosterone (RAA) antagonists and novel anticoagulants. Avoidance of such tools may exceed true risks, as thresholds of renal dysfunction for exclusion are only loosely substantiated, and clinicians sooner tolerate sins of omission than those of commission. To a degree difficult to measure, perception of patients with CKD as doomed can become self-fulfilling prophecy by influencing withholding of tests and therapies, so-called "therapeutic nihilism."

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Second, the extent of CVD in CKD reflects a significant overlap in risk factors for atherosclerosis, in particular hypertension and diabetes mellitus. Progressive nephropathy, associated with increasing risk for cardiovascular death,[5] is also associated with increasing chronicity of hypertension and diabetes. CKD may be a marker for cumulative vascular injury, and poor outcomes the result of a greater extent and duration of disease. Overlap in risk factors appears to interact importantly with racial disparities in both incident CKD and cardiovascular death, with a disproportionate burden of both among American blacks.[6,7]

Third, on which this review focuses, it is possible that elements of the pathophysiology of CKD itself potentiate progression of CVD and adverse outcomes. Beyond traditional CVD risk factors, the consequences of progressive renal dysfunction, including disorder of sodium and water homeostasis, RAA and sympathetic nervous system activation, anemia, disorder of bone and mineral metabolism, disorder of potassium homeostasis, uremia, and toxins, may contribute directly to CVD. Understanding the relationship between these disturbances and CVD progression may inform novel approaches to therapy in patients with established CKD, and more importantly, may inspire increased emphasis on CKD prevention.

TRADITIONAL RISK FACTORS

In part, CKD is a marker for presence of traditional CVD risk factors.

Independent risk factors for coronary heart disease identified in the Framingham Heart Study—age, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), blood pressure, diabetes, and smoking—all have been associated with risk for CKD.[8,9] In turn, compared with the general population, individuals with advanced CKD more often exhibit diabetes, hypertension, low physical activity, low HDL-C, and hypertriglyceridemia, controlling for age, race, sex, and atherosclerotic CVD.[10]

Traditional risk factors alone cannot completely explain CVD risk in CKD. In a pooled analysis of 577 women and 357 men with CKD in the Atherosclerosis Risk in Communities (ARIC) study and Cardiovascular Health Study (CHS), Framingham scores underestimated risk for cardiac events at 5 and 10 years.[11]

An instructive example comes from experience with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) in advanced CKD. Whereas the prospective Dialysis Outcomes and Practice Patterns Study (DOPPS) suggested significant reduction in cardiovascular and non-cardiovascular death in association with statin use,[12] randomized comparisons of statin versus placebo in the Deutsche Diabetes Dialyse Studie (4D) trial[13] and the larger A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA) showed no significant difference in the composite of cardiovascular death, MI, and stroke.[14] Most recently, the Study of Heart and Renal Protection (SHARP) did show a benefit of combination statin ezetimibe therapy for incidence of a first major atherosclerotic event (non-fatal MI or coronary death, non-hemorrhagic stroke, or any arterial revascularization procedure).[15]

Taken together, these data suggest statins may reduce atherosclerotic events in patients with CKD, but evidence for reduction in mortality remains elusive. Multiple explanations for this may be considered. CKD may lead to cardiovascular mortality through pathways independent of statins. Statins might be expected to have less effect on incidence of SCA, which accounted for 34% of events in 4D. None of the above trials included CHF endpoints. Alternatively, CKD may attenuate or alter the physiological effect of statins. Awareness of a residual CVD risk in CKD, incompletely explained by traditional risk factor and insufficiently reduced by risk factor modification, motivates an analysis of the several facets of CKD pathophysiology contributing to CVD progression and mortality.[16]

THE KIDNEY IN HEALTH AND DISEASE

Insight into the consequences of renal dysfunction may be gleaned from review of the kidney's normal function. In health, the normal kidney shoulders several responsibilities, including regulation of salt and water homeostasis, vascular tone (via renin, activating angiotensin, and, in turn, aldosterone), oxygen-carrying capacity (via erythropoietin, stimulating bone marrow production of red blood cells), bone and mineral metabolism (via phosphate excretion and 1α-hydroxylase, activating 25-hydroxyvitamin D), potassium regulation, and elimination of drugs and toxins. Each of these pathways may contribute to CVD.

Sodium and Water Balance

Altered salt and water handling in CKD predisposes to volume retention and secondary alterations in vascular tone that together contribute to hypertension. Responsiveness to both exogenous diuretics and endogenous natriuretic peptides is reduced. When partially nephrectomized dogs or humans with stage 5 CKD are subjected to a dietary salt load, mean arterial pressure increases.[17,18] Elevation in blood pressure is initially explained by expansion of extracellular fluid volume, with a commensurate rise in cardiac output. Subsequently, however, cardiac output returns to baseline, while arterial pressure remains elevated, consistent with an increase in total peripheral resistance.[19] Augmentation in systemic vascular tone is mediated by activation of