Cardiovascular Disease Risk in Children With Kidney Disease

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Summary: Cardiovascular disease is a major cause of death in individuals diagnosed with kidney disease during childhood. Children with kidney disease often incur a significant cardiovascular burden that leads to increased risk for cardiovascular disease. Evidence has shown that children with kidney disease, including chronic kidney disease, dialysis, kidney transplantation, and nephrotic syndrome, develop abnormalities in cardiovascular markers such as hypertension, dyslipidemia, left ventricular hypertrophy, left ventricular dysfunction, atherosclerosis, and aortic stiffness. Early identification of modifiable risk factors and treatment may lead to a decrease of long-term cardiovascular morbidity and mortality, but evidence in this population is lacking.
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Kidney disease among adults is recognized as a risk factor for the development of adverse outcomes caused by cardiovascular disease (CVD). Overall, CVD is the leading cause of mortality of individuals with CKD in developed countries. According to the US Renal Data System 2017 report, 65.8% of adults age 66 years and older with chronic kidney disease (CKD) have CVD, more than twice the prevalence of CVD in individuals without CKD (31.9%).[1] In fact, individuals with CKD have higher rates of atherosclerotic heart disease, acute myocardial infarctions, congestive heart failure, and atrial fibrillation among other cardiovascular-related conditions. Ultimately, individuals with CKD are more likely to die from CVD than to progress to end-stage renal disease (ESRD).[2] The risk of cardiovascular death increases with worsening kidney function and individuals with kidney disease have a markedly decreased life expectancy. Mortality in patients on dialysis is reported to be 10 to 30 times higher than the general population, and for kidney transplant recipients the prevalence is twice as high compared with the general population.[3,4]

As in adults, children with kidney disease are at increased risk for CVD-related mortality. According to the US Renal Data System 2017 Annual Report, the CVD mortality rate for children and adolescents younger than age 21 years with ESRD was 8 per 1,000 patient years, with the highest rates among children on dialysis (Fig. 1).[1] Individuals with ESRD on dialysis during childhood are expected to live 42 to 53 years less than the general population. Even with renal transplantation, life expectancy is 15 to 20 years shorter than that of the general population.[1] Furthermore, children with kidney disease often carry a significant cardiovascular burden that may not clinically manifest during childhood as it does in adulthood (ie, myocardial infarction, angina, cerebrovascular disease). There is mounting evidence that children with kidney disease incur high rates of CVD risk factors such as hypertension and dyslipidemia and develop abnormalities in subclinical surrogate markers of CVD, including left ventricular hypertrophy (LVH), left ventricular dysfunction, atherosclerosis, aortic stiffness, and endothelial dysfunction.

The American Heart Association and the National Institutes of Health Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction have placed children with kidney disease in the highest risk stratification for the development of CVD, emphasizing the magnitude of this issue and the importance of prevention and treatment.[5,6] Over the past several years, advancements have been made in our understanding of the link between kidney disease and the development of CVD, particularly in the pediatric population. In this article, we review recent evidence on the risk factors for CVD, subclinical markers of CVD, and management of children with kidney disease including CKD (stages 2-5), dialysis, kidney transplantation, and nephrotic syndrome.

PATHOGENESIS OF CVD

The pathophysiology of CVD in children with kidney disease is multifactorial, involving both traditional and

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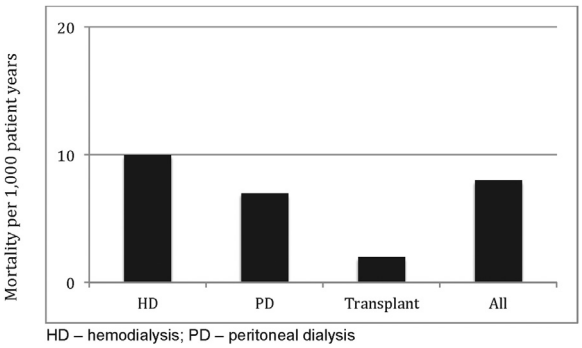

Figure 1. Cardiovascular mortality rates in incident pediatric patients with end-stage renal disease by modality from 2010 to 2014.[1]

kidney-related risk factors (Fig. 2). Traditional risk factors include modifiable elements such as hypertension, dyslipidemia, obesity, poor diet/physical activity, and abnormal glucose metabolism.[5] Interestingly, children without traditional risk factors are still at an increased risk of mortality from CVD, suggesting that nontraditional risk factors play an important role.[7] Risk factors specific to kidney disease include albuminuria, decreased glomerular filtration rate (GFR), anemia and thrombogenic factors, to name a few. Dysregulation of bone-mineral homeostasis, specifically alterations in calcium, phosphorous, and hyperparathyroidism, is linked strongly to CVD in adults and is considered a major risk factor for cardiovascular events. Increased levels of fibroblast growth factor 23 (FGF-23) also have emerged as a novel bone-mineral risk factor for CVD among individuals with kidney disease. Although traditional and kidney-related CVD risk factors have been shown to be associated with cardiovascular mortality in adults, studies linking these factors with mortality in children are lacking.

The interactions between kidney disease and CVD are inter-related because kidney disease is a known risk factor for CVD and CVD has been shown to be a risk factor for the development and progression of kidney disease (Fig. 3). The toll of the cardiovascular burden has direct negative effects on the myocardium and vasculature, potentially leading to clinical cardiovascular events such as ischemic heart disease, cerebrovascular disease, heart failure, and death. However, events such as these are rare in childhood and children with kidney disease may instead manifest subclinical indicators of cardiomyopathy and vascular disturbance that may be used as surrogate markers for CVD.

Traditional Risk Factors	Kidney Disease-Related Risk Factors
Family history of cardiovascular disease	Albuminuria
Age	Reduced glomerular filtration rate
Gender	Dialysis Modality
Nutrition/diet	Anemia
Physical inactivity	Fibroblast Growth Factor-23 (FGF-23)
Tobacco exposure	Calcium/Phosphate mineral dysregulation
Hypertension	Hyperparathyroidism
Dyslipidemia	Homocysteine
Overweight/obesity	Fluid volume overload
Metabolic syndrome	Altered nitric oxide/endothelin balance
Inflammatory markers	Lipoprotein abnormalities
Perinatal factors	Sleep disorder
	Thrombogenic factors

Figure 2. Traditional and nontraditional risk factors in children with kidney disease.

The strain of pressure and volume on the myocardium associated with traditional and kidney-related CVD risk factors eventually leads to cardiomyopathy. Early markers of cardiomyopathy may be diagnosed by echocardiography. Remodeling of the myocardium results in LVH and structural changes of the geometry of the heart (concentric and eccentric hypertrophy). Concentric hypertrophy is seen in response to increased afterload and eccentric hypertrophy develops in response to increased preload, suggesting multiple factors contribute to the development of LVH.[8] Systolic and diastolic dysfunction of the left ventricle also are found in children with kidney disease.

Vascular disturbances manifest as atherosclerosis, arteriosclerosis, and endothelial dysfunction. The vascular changes associated with kidney disease result in increased afterload that exacerbates LVH. LVH, in turn, increases myocardial oxygen demand on the vasculature, ensuing in an inter-related cycle. Atherosclerosis typically is characterized by the patchy discontinuous accumulation of fatty plaques within the tunica intima of the arterial walls, which can lead to plaque rupture and subsequent vessel occlusion. However, individuals with kidney disease often present with calcification in the media layer of the vessels (also referred to as *Monckeberg's sclerosis*). Increased carotid intima-media thickness (cIMT) and calcification of vessels by computed tomography (CT) scan are known to be early indicators of atherosclerosis. cIMT is a noninvasive technique that uses B-mode ultrasound to measure the thickness of the intimal plus medial layers of vessels. Both modalities have been shown to be accurate predictive measures of risk of future cardiac events in adults.[9,10] Arterial pulse-wave velocity (PWV) is an early marker for arteriosclerosis, or arterial stiffness, which is also an independent predictor of CVD in adults.[11] PWV is a noninvasive measure of the speed at which pulses move from one point to another in the arterial system using applanation tonometry. As arterial stiffness develops and progresses, the velocity of blood flow increases, therefore increasing the PWV. Altered nitric oxide (NO)/endothelin balance results in endothelial dysfunction, which can be tested with occlusion vascular reactivity and brachial artery reactivity testing.

The next section focuses on major CVD risk factors and subclinical cardiac and vascular surrogate markers in specific groups of children with kidney disease, that is, CKD stages G2 to 5, dialysis, kidney transplant, and nephrotic syndrome.