

Cardiovascular Disease in Children with Chronic Kidney Disease

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ABSTRACT

More than a decade ago, cardiovascular disease (CVD) was recognized as a major cause of death in children with advanced CKD. This observation has sparked the publication of multiple studies assessing cardiovascular risk, mechanisms of disease, and early markers of CVD in this population. Similar to adults, children with CKD have an extremely high prevalence of traditional and uremia-related CVD risk factors. Early markers of cardiomyopathy, such as left ventricular hypertrophy and dysfunction, and early markers of atherosclerosis, such as increased carotid artery intima-media thickness, carotid arterial wall stiffness, and coronary artery calcification, are frequently present in these children, especially those on maintenance dialysis. As a population without preexisting symptomatic cardiac disease, children with CKD potentially receive significant benefit from aggressive attempts to prevent and treat CVD. Early CKD, before needing dialysis, is the optimal time to both identify modifiable risk factors and intervene in an effort to avert future CVD. Slowing the progression of CKD, avoiding long-term dialysis and, if possible, conducting preemptive transplantation may represent the best strategies to decrease the risk of premature cardiac disease and death in children with CKD.

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Current registry data from the National Center for Health Statistics indicate that overall mortality rates in the general US pediatric population were 0.31 per 1000 population for children aged 1–19 years in 2008.¹ In contrast, these rates were 35.6 (dialysis) and 3.5 (transplant) per 1000 patient-years at risk for children aged 0–19 years with ESRD according to 2006–2008 data from the US Renal Data System (USRDS).² These large discrepancies in mortality rates exist despite the widespread availability of state-of-the-art renal replacement therapy and substantial advances in the care of children with CKD over the last 3 decades. Even more disturbing is the fact that for dialyzed children, all-cause mortality rates have not changed significantly since the 1980s, with the highest

rates reported in children on maintenance dialysis who have never received a kidney transplant (Table 1). Furthermore, young adults developing ESRD during childhood have a significantly diminished life expectancy. Upon reaching adulthood, dialysis patients live 40–50 years less, and transplant patients live approximately 20–25 years less, compared with an age- and race-matched US population.²

In 1998, the National Kidney Foundation Task Force on Cardiovascular Disease declared an epidemic of cardiac disease in ESRD patients.³ Cardiovascular disease (CVD) mortality was especially high in young adults (aged 25–34 years) receiving maintenance dialysis, who died at a rate >100 times higher than the comparably aged general population. Although the task force focused only on adults, it raised

important questions regarding pediatric patients with ESRD. Do they have cardiac disease? Do they die from cardiac disease? If so, how significant is the problem? This review summarizes the most current literature describing the epidemiology of CVD in children with CKD.

CARDIOVASCULAR MORTALITY IS THE LEADING CAUSE OF DEATH IN CHILDREN WITH CKD

After the task force publication, Parekh *et al.*⁴ used the USRDS database to evaluate the risk of cardiac death in children and young adults (aged 0–30 years) in 2002. Of 1380 deaths recorded between 1990 and 1996, 311 (23%) were due to cardiac causes. These data are in sharp contrast to the general pediatric population, in which CVD mortality is very low and accounts for <3% of all deaths.¹

Subsequent reports from international registries confirm that CVD is the leading cause of death in both children with ESRD and in adults with childhood onset of CKD. The Australia and New Zealand Dialysis and Transplant,⁵ Dutch national cohort study,⁶ and a large German study⁷

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Table 1. Annual mortality rates per 1000 patient-years at risk, period prevalent patients aged 0–19 years adjusted by sex, race, ethnicity, primary diagnosis, and patient vintage

	1980–1989	1990–1999	2000–2008
Hemodialysis	64	61	59
Peritoneal dialysis	83	75	80
Dialysis/never transplanted	126	151	134
Transplants	33	16	9

Data are from the USRDS (2011).²

reported that 40%–50% of all deaths are from cardiovascular or cerebrovascular causes.

More current USRDS data reconfirmed CVD as one of the major causes of death in children with CKD (Figure 1). Cardiovascular death rates are similar in children on peritoneal dialysis and hemodialysis, whereas transplant recipients have a relatively lower risk of cardiac death.² The most recent USRDS analysis of long-term survival in 18,911 patients who received a first kidney transplant during childhood (at <21 years old, 1983–2006) showed that the majority of deaths were from cardiovascular causes. Most of these deaths occurred in patients who had graft failure (45%), rather than in those with a functioning graft (25%).⁸ Furthermore, the hazard ratio was 7.8 for patients with cardiovascular mortality associated with dialysis

after graft failure relative to those patients with a functioning graft. In agreement with prior studies, this recent report also noted decreased cardiovascular mortality in transplant recipients in the most recent era. However, even in these patients, the mortality rates are still significantly higher (approximately 10 times) than in the general pediatric population.

In older adults with ESRD, coronary artery disease (CAD) and cardiomyopathy-associated congestive heart failure are the leading causes of CVD mortality. The most common causes of ESRD in adults are diabetes and hypertension, two conditions having a strong association with other cardiovascular risk factors. Conversely, children have neither diabetes nor symptomatic atherosclerosis at the time of CKD diagnosis, possibly explaining why the causes of cardiac death in children are different from those in adults

(Table 2). In looking more closely at cardiovascular deaths in children with CKD, cardiac arrest is the most common cause, followed by arrhythmia, cardiomyopathy, and cerebrovascular disease, with myocardial infarction rarely reported.²

The prevalence of cardiac arrest in the youngest age group (0–4 years) is 5–10 times higher than in other pediatric age groups, perhaps reflecting the difficulty of ascertaining the true cause of sudden death in young children. These data may be confounded by comorbid conditions such as congenital disorders, which are not included in the USRDS database. As with mortality, a USRDS analysis of cardiac morbidity in children on maintenance dialysis confirms that cardiac disease in children is different from adults. A total of 1454 Medicare incident pediatric dialysis patients (aged 0–19 years) were identified from 1991 to 1996.⁹ Among them, 452 patients (31.2%) developed a cardiac-related event. Arrhythmia was most common (19.6%), followed by valvular disease (11.7%), cardiomyopathy (9.6%), and cardiac arrest (3%).

CHILDREN WITH CKD ARE THE PEDIATRIC POPULATION WITH THE HIGHEST CARDIOVASCULAR RISK

Although symptomatic CAD is rarely noted in children with CKD, atherosclerosis is already evident in children with advanced kidney disease. One small study from Turkey reported histopathological findings of internal iliac artery samples obtained at the time of kidney transplantation in 12 children.¹⁰ The authors showed that 5 of 12 arteries had evidence of atherosclerosis or arteriosclerotic lesions, including fibrous or fibroelastic intimal thickening, disruption of the internal elastic lamella, and atheromatous plaques. This evidence of early and accelerated atherosclerosis and arteriosclerosis likely explains why young adults with childhood onset of CKD are at increased risk for symptomatic CAD.

Not surprisingly, the American Heart Association's guidelines for cardiovascular risk reduction in high-risk pediatric

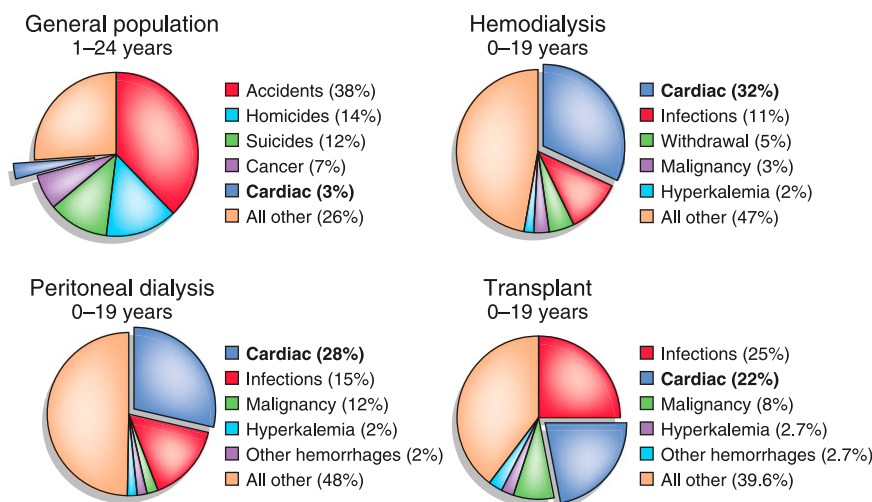


Figure 1. Leading causes of death in general pediatric population and in children on renal replacement therapy. Data are presented as percentages. Data for dialysis and transplant patients are from the USRDS (2011).² Data for general pediatric population are from Mathews et al. (2011).¹

Table 2. Causes of cardiac death in children 0–19 years of age with CKD

Dialysis	Transplant
Cardiac arrest/arrhythmias	Cardiac arrest/arrhythmias
Cerebrovascular disease	Cerebrovascular disease
Congestive heart failure/pulmonary edema	Acute myocardial infarction
Cardiomyopathy	Cardiomyopathy
Acute myocardial infarction	
Pericarditis	

Data are from the USRDS (2011).²

patients stratified pediatric CKD patients in the highest risk category for the development of CVD.¹¹ This group includes those with pathologic and/or clinical evidence for manifestations of coronary disease before age 30 years. In addition to CKD, this highest risk category includes the following four other conditions: homozygous familial hypercholesterolemia, type 1 diabetes mellitus, heart transplantation, and Kawasaki disease with coronary aneurysms. However, even among these conditions, there is a wide variability in cardiovascular risk. For example, studies in young adults with childhood-onset type 1 diabetes—a condition that, like CKD, is not associated with primary heart disease—show that CVD-related death is very rare during the first 3 decades of life. Specifically, two large studies from Europe^{12,13} reported acute metabolic complications as the leading cause of death before age 30 years, whereas CVD was predominant after age 30 years. Another recent analysis of short-term mortality (mean follow-up 15.8 years) of young patients with childhood onset of type 1 diabetes

from Italy reported no cardiac causes of deaths in the entire cohort.¹⁴

PREVALENCE OF CARDIOVASCULAR RISK FACTORS IN CHILDREN WITH CKD IS SIMILAR TO THAT IN ADULTS WITH CKD

Children with CKD are at very high risk for the development of accelerated atherosclerosis, arteriosclerosis, and premature CVD during young adulthood due to a unique combination of traditional and uremia-related risk factors (Table 3).

Traditional Risk Factors

Recent evidence highlights the high prevalence of traditional cardiovascular risk factors in children with even early stages of CKD. The Chronic Kidney Disease in Children (CKiD) study, an observational cohort of 586 children (aged 1–16 years) with stage 2–4 CKD, provides contemporary data on cardiovascular risk factors in this population. On enrollment, hypertension was present in 54% of

participants.¹⁵ Despite the use of antihypertensive medication, 48% of these children were found to have inadequately controlled BP. Equally concerning, analysis of ambulatory BP monitoring data¹⁶ showed a high frequency of masked hypertension (38%), a rate four to five times higher than reported in unselected patients referred to pediatric hypertension clinics (7%–11%).^{17,18}

In terms of other traditional risk factors, dyslipidemia was found in 45% and obesity in 15% of the CKiD cohort.^{19,20} As mentioned earlier, although diabetes is very rare cause of CKD in children, hyperinsulinemia and insulin resistance are present in 9% and 19%, respectively, of the CKiD population.²⁰ Importantly, almost one-half of patients in the CKiD cohort have a combination of traditional risk factors. Even nonobese patients have a high prevalence of multiple traditional cardiovascular risks, with nearly one-quarter having two or three cardiovascular risk factors. Overweight or obese study participants have very high prevalence of multiple risk factors, similar to rates in severely obese (body mass index >40 kg/m²) children without kidney disease. This pattern differentiates the population of children with CKD from healthy children, in whom the coexistence of multiple cardiovascular risk factors is extremely infrequent, and is restricted to those who are obese (metabolic syndrome). The prevalence of these traditional risk factors increases as CKD progresses, and is highest in children on maintenance dialysis (Table 3). Although successful kidney transplantation leads to elimination of many uremia-related risk factors for atherosclerotic CVD (see below), transplant recipients remain at high risk for CVD from these traditional risk factors (Table 3). For example, a recent multicenter study determined that 38% of kidney transplant recipients had at least three traditional cardiovascular risk factors.²¹

Uremia-Related Risk Factors

The high prevalence of traditional risk factors may account for the accelerated CAD and premature cardiac death noted in young adults with a history

Table 3. Common risk factors for CVD in children with CKD

Risk Factors	CKD (%) ^a	Dialysis (%)	Transplant (%)	References
Traditional				
hypertension	47–54	52–75	63–81	15,21,25,31,54–58
dyslipidemia	45	33–87	55–84	19,21
obesity	15	8–11	12–22	20,21,25,59
hyperglycemia	4	11	22	20,21
Uremia related				
anemia	38–48	40–67	32–64	22,23,25,57,60–62
hyperparathyroidism	21	72		57,63
increased calcium-phosphorus product		53–55		25,62
increased C-reactive protein		76		64
hypoalbuminemia	47	40–60		62,57

^aData are from CKiD study^{15,19,20} and North American Pediatric Renal Trials and Collaborative Studies registry.^{23,54,57}

of childhood-onset CKD. However, these risk factors do not fully explain the high rates of cardiac death in children aged 0–19 years on maintenance dialysis or in those receiving a kidney transplant. To better understand the increased risk of cardiac disease in these children, investigators have focused on uremia-related risk factors.

As in adults, abnormal mineral metabolism is common in children with CKD, a finding that becomes more frequent as kidney function decreases (Table 3). Despite the widespread use of erythropoiesis-stimulating agents and iron therapy, anemia is poorly controlled, especially in children with advanced CKD²² or in those on maintenance dialysis.²³ Anemia in these children has been linked to overall mortality, but not to cardiac-related death.²⁴ Inflammation is also likely a contributing risk factor in children receiving chronic dialysis (Table 3), although no study has examined the role of inflammation in cardiac death in these young patients.

As with traditional risk factors, there is frequently a coexistence of CKD-related risk factors in children. A cross-sectional analysis of all pediatric maintenance hemodialysis patients (aged 0.7–18 years, $n=656$) using data from the Centers for Medicare and Medicaid Services ESRD Clinical Performance Measures Project²⁵ shows that 38% have anemia, 63% have serum phosphorus >5.5 mg/dl, and 55% have calcium-phosphorus product ≥ 55 mg²/dl.²

Despite the data presented above, no study has directly linked traditional and/or uremia-related risk factors with CVD mortality. However, the remarkable decrease in mortality after kidney transplant, compared with continued dialysis, clearly indicates that the uremic milieu is a major cause of cardiac death in children with CKD (Table 1).

INTERMEDIATE CARDIOVASCULAR OUTCOMES

Recent research has focused on identifying the presence of early cardiovascular abnormalities in children with CKD. Left ventricular (LV) abnormalities such as LV hypertrophy (LVH) and LV dysfunction, damage to the large arteries such as stiffness and increased intima-medial thickness (IMT) of the carotids, and coronary calcifications are now accepted as early markers of cardiomyopathy and atherosclerosis. These markers are strong, independent predictors of cardiac morbidity and mortality, both in the general population and in adults with CKD. Furthermore, over the last decade, these abnormalities have also been noted in children and young adults with CKD (Table 4).

LVH IS THE MOST COMMON CARDIAC ABNORMALITY IN CHILDREN WITH CKD

Although most pediatric studies evaluating LV structure are cross-sectional and include few patients, they consistently show that LVH develops even when CKD is mild and progresses as kidney function deteriorates.^{26,27} Larger, more recent, multicenter studies in children with stage 2–4 CKD, on dialysis, and post-transplant have confirmed these previous investigations. The baseline CKiD data¹⁶ demonstrate an overall 17% prevalence of LVH. LVH is more frequent in children with sustained (both casual and ambulatory) (34%) and masked (20%) systolic or diastolic hypertension compared with children with normal casual and ambulatory BP (8%). At initiation of maintenance dialysis, 69%–82% of pediatric patients have evidence of LVH.^{28,29} LVH persists (40%–85%) during long-term dialysis^{28,30} with both concentric

and eccentric geometric patterns of LVH present in these patients. Data from the International Pediatric Peritoneal Dialysis Network registry³¹ on 507 patients report the overall prevalence of LVH to be 48%. A Midwest Pediatric Nephrology Consortium study,²¹ utilizing data from six centers, demonstrated the prevalence of LVH to be 40% in children 1-year post-transplant. Most of these studies show the persistence of cardiac hypertrophy,^{32–34} but some report improvement post-transplant.³⁵

As in adults, hypertension is the main cause of cardiac hypertrophy in children before ESRD or post-transplant. Elevated parathyroid hormone (PTH) might contribute to progression of LVH in children with stage 2–4 CKD³⁶ and hypertension associated with volume overload has been linked to the development of LVH in the dialysis population.²⁹

CHILDREN ON MAINTENANCE DIALYSIS ARE AT HIGHEST RISK FOR LV DYSFUNCTION

Tissue Doppler imaging demonstrates impaired LV filling and compliance early in the progression of pediatric CKD.³⁷ The prevalence of diastolic dysfunction increases in patients undergoing maintenance dialysis.³⁷ The functional consequence of these changes has been suggested by a recent study linking diastolic dysfunction to altered maximal aerobic capacity.³⁸

Several reports using echocardiography document subtle alterations in LV wall mechanics, especially in children on maintenance dialysis. These alterations include decreased shortening at the myocardial mid-wall,^{39,40} depressed contractile reserve during stress/exercise,^{26,41} and acute reductions in global and segmental myocardial blood flow with a concomitant increase in myocardial stunning.⁴²

ARTERIAL ABNORMALITIES DEVELOP DURING EARLY CKD

As with LV structure and function, vascular changes such as an increase in carotid IMT (cIMT) and arterial stiffness (pulse

Table 4. Common early cardiac and vascular abnormalities in children with CKD

	Stage 2–4 CKD (%)	Dialysis (%)	Transplant (%)	References
LVH	17–50	30–92	8–82	16,27,30,31,35,65–67
Abnormal cIMT	29–61	66–89	58–75	43,44,46,68–73
CAC	—	12–20	—	7,45–47,74–77

wave velocity) begin at predialysis stages of CKD^{33,43} and are worst in children on maintenance dialysis^{33,43} (Table 4). There are some reports suggesting improvements in these arterial abnormalities post-transplant.^{44,45} In children with stage 2–4 CKD, increased cIMT is associated with hypertension and dyslipidemia. Unlike in predialysis CKD, abnormal mineral metabolism (high phosphorus, calcium-phosphorus product, and PTH) is the major predictor of vascular changes in children on dialysis. A recent study suggests that both low and high levels of 1,25-dihydroxyvitamin D are associated with high cIMT.⁴⁶ These apparently contradictory relationships may be due to both the effects of vitamin D on calcium-phosphorus homeostasis and its proinflammatory properties.⁴⁴

CORONARY ARTERY CALCIFICATION IS FREQUENT IN CHILDREN ON MAINTENANCE DIALYSIS

An early autopsy study of pediatric patients with ESRD who died between 1960 and 1983 showed a high prevalence of vascular calcinosis.⁴⁷ In this study, coronary artery calcification (CAC) was present in 28%. Peak calcium-phosphorus product, peak serum P, and cumulative dose of calcitriol were significantly associated with the severity of the calcinosis. Despite significant advances in the care of children with ESRD since the autopsy study, the frequency of CAC has not changed much (Table 4). As in the above study, higher time-integrated serum phosphorus, calcium-phosphate product, PTH, and the amount of cumulative calcium-containing oral phosphate binders predict the presence of CAC in recent reports. As in adults, cardiac valve calcification is also described in children on maintenance dialysis.⁴⁸ However, in a study of 40 young adults (mean age 23.6 years) who developed ESRD at mean age of 11.5 years, cIMT is similar to healthy controls and only 4 (10%) patients have evidence of coronary calcification.⁴⁵ The authors noticed this relatively low rate of cardiac calcification compared with

other studies might be explained by a significantly lower amount of prescribed calcium-containing phosphate binders and vitamin D preparations in their patients.

In the decade since the recognition of CVD as a major cause of morbidity and mortality in children with CKD, there has been important progress in our understanding of the mechanisms leading to the development of early cardiac and vascular abnormalities in these patients. Yet the vast majority of data come from observational (registries) or small, cross-sectional studies. There have been no high-quality studies evaluating the association of early markers/intermediate outcomes of CVD during childhood and cardiac morbidity and mortality later in life. Nor have there been any interventional studies on controlling modifiable cardiovascular risks in children with CKD.

Despite these gaps in the literature, existing data on cardiovascular risks, early cardiac and vascular abnormalities, and CVD morbidity and mortality all point to dialysis vintage as a major factor associated with poor outcomes in children with ESRD.^{2,8} Therefore, primary among all management strategies in childhood CKD/ESRD is the avoidance of long-term dialysis, ideally with preemptive transplantation when feasible. Although cardiovascular risk remains high relative to the general population, successful transplantation can significantly improve uremia-related risk factors and, most importantly, increase life expectancy by age 20–30 years compared with long-term dialysis.

For those children who are unwilling or unable to receive a kidney transplant, several strategies should be used to reduce the cardiovascular risks associated with maintenance dialysis. Aggressive monitoring and management of hypertension, dyslipidemia, mineral metabolism, anemia, nutrition, and inflammation cannot be overemphasized. Unfortunately, the prescription of adequate dialysis, as measured by Kt/V, will not necessarily decrease the risk associated with these CKD-associated complications. Pediatric data from the Centers for Medicare and Medicaid Services End-Stage Renal Disease Clinical Performance Measures

(CPM) Project^{25,49} indicate that 89% of patients receiving hemodialysis and 87% of patients receiving peritoneal dialysis achieved the recommended modality-specific Kt/V. Yet, one-third of children had significant anemia, almost one-half had low serum albumin, and two-thirds had uncontrolled hypertension and a high calcium-phosphorus product.

These studies, supported by epidemiologic data on cardiac death in peritoneal dialysis and hemodialysis patients, clearly indicate that current dialysis practice guidelines based primarily on Kt/V will not decrease CVD morbidity and mortality in children with ESRD. Unfortunately, unlike in adults,⁵⁰ there have been no randomized studies in pediatric patients examining the role of alternative dialysis strategies (quodidian hemodialysis) to improve cardiac outcomes. However, small, single-center studies have shown clinically important improvements in cardiac hypertrophy and function when children receive dialysis more frequently than the traditional, thrice-weekly in-center schedule.^{51,52} Considering the potential for a longer and possibly more productive life, the benefits of more frequent and longer dialysis treatment might therefore be more far reaching in children than in adults.⁵³

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DISCLOSURES

None.

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