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REVIEW

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Cardiovascular complications in pediatric end-stage renal disease

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Abstract Mortality from end-stage renal disease (ESRD) is often due to cardiac causes. Although cardiovascular complications of ESRD have long been recognized, only recently has the presence of traditional cardiovascular risk factors been associated with late cardiovascular complications. This review presents a history of cardiac involvement in ESRD, the pathophysiology of accelerated atherosclerosis and left ventricular hypertrophy, and a summary of the literature on cardiovascular risk assessment in children. Techniques for non-invasive assessment of cardiac end-organ injury are also discussed. Recommendations for monitoring of risk factors and treatment in the pediatric ESRD population are presented.

Keywords Cardiovascular complications · End-stage renal disease

Introduction

Cardiac complications of end-stage renal disease (ESRD) have assumed increasing importance, as cardiac disease now accounts for the majority of deaths in adults with ESRD, and about a quarter of pediatric ESRD deaths [1, 2, 3] (Fig. 1). The current literature describes a wide array of cardiovascular complications of ESRD, but there is little information on the natural history or efficacy of interventions to prevent cardiovascular complications. In particular, increasing attention has been paid to coronary artery disease and left ventricular (LV) dysfunction secondary to the presence of major cardiovascular risk factors after the onset of renal insufficiency. This manuscript will review the natural history of cardiac involvement with ESRD, with an emphasis on acquisition of morbidity secondary to sustained exposure to cardiovascular risk factors. Recommendations for evaluation and management to minimize life-long risk in pediatric patients will also be presented.

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Interactions of ESRD with cardiac disease

Historically, cardiovascular complications were approached as either acute events requiring management or sequelae of ESRD itself where treatment of the underlying disease was the most prudent course. For example, arrhythmias were considered secondary to electrolyte imbalance from ESRD and congestive heart failure secondary to severe fluid retention. LV dilation and hyper-

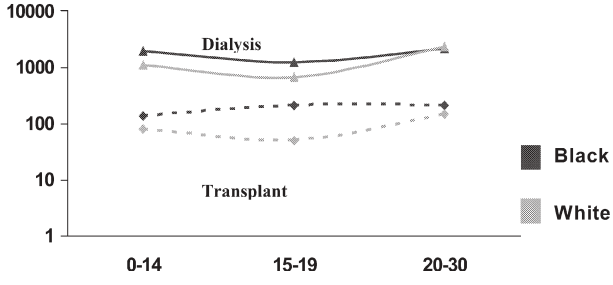

Fig. 1 Cardiovascular mortality in pediatric end-stage renal disease (ESRD) according to dialysis modality and race (USRDS 1990–1996). Adapted from Ref. [1]

trophy were also considered inevitable complications of hypertension, and management of hypertension was not focused on preventing complications. Over the last 2 decades, innovations in clinical management and associated improvements in outcome have suggested the need to revise this older paradigm. For example, introduction of erythropoietin prevented chronic severe anemia, and consequently prevented compensatory LV dilation [4] and reduced the prevalence of LV hypertrophy. Thus, anticipatory management could prevent known long-term cardiovascular complications.

Success with renal replacement therapy has lengthened life expectancy. Currently, mortality in patients with ESRD is not only related to renal replacement therapy but also to chronic diseases in other organ systems as a result of prolonged exposure to risk factors, particularly with regard to cardiovascular disease. Paradoxically, renal replacement therapy by either dialysis or transplantation may potentiate cardiovascular risk at the same time as it corrects underlying abnormalities of renal function. Management of renal failure alone is no longer the only determinant of long-term survival, and it is now critical to focus on co-morbid conditions to improve survival.

The cardiac abnormalities associated with ESRD are diverse. These include pericardial disease, arrhythmias, abnormalities of LV function, and coronary artery disease [1, 2]. Pericardial disease is most likely secondary either to the underlying cause of the renal disease or pro-inflammatory aspects of uremia [5]. Arrhythmias may be secondary to electrolyte imbalance, cardiomyopathy, and effects of medications or dialysis on myocardial repolarization. LV dysfunction is secondary to chronic anemia, hypertension, intravascular volume stresses (including fistulae for dialysis), and uremia [6, 7]. Coronary artery disease is secondary to the clustering of traditional cardiovascular risk factors (hypertension, dyslipidemia for example), as well as the presence of a pro-inflammatory state and endothelial dysfunction [8, 9, 10, 11]. In addition, novel risk factors such as C-reactive protein (CRP), lipoprotein (a) [Lp(a)], thrombotic factors, and homocysteine are impacted adversely by ESRD [10, 11, 12]. Of hospitalizations in pediatric patients with ESRD, 20% are reported to be due to arrhythmias, 10% to cardiomyopathy, and 3% to a cardiac arrest [13]. The incidence of cardiomyopathy has also doubled over the 6 years from 1991 to 1996 (Fig. 2) [13].

Vascular injury

Vascular endothelium is the initial target for the proliferation of the atherosclerotic process [14]. Damage to the endothelium initiates a cycle of vascular smooth muscle proliferation and deposition in the intimal region of the vessel leading to fatty streak and plaque formation [14] (Fig. 3). This process of atherosclerosis results in "atheromas" in the intima of the vessel wall. There is reported subclinical evidence of atherosclerosis with intimal plaques in pediatric ESRD. In a series of children with iliac artery biopsy at the time of transplant, atherosclerosis in the uropathy group was also associated with increased serum calcium [15]. In otherwise healthy individuals, it is unusual for calcium to be incorporated into atherosclerotic plaques before the 4th or 5th decade of life.

Atherosclerosis is the most common form of arteriosclerosis but is only one form of arteriosclerosis. Arteriosclerosis is a group of diseases characterized by thickening and loss of elasticity of the arterial wall [16]. This is an important distinction especially in ESRD, as both forms are reported to occur in ESRD, and may have differing pathogenesis. Medial vessel calcification and arteriosclerosis or Monckeburg arteriosclerosis have also been shown in the pediatric ESRD population by vascular calcification in the coronaries, aorta, peripheral vessels, and aortic valves. Autopsy series of subjects with ESRD revealed soft tissue calcification in 60% of pediatric patients; 50% were on dialysis at the time of death [17]. Arteriosclerosis has also been described in a small series of patients, with four of eight patients having evidence of arteriosclerosis and diffuse vascular calcification and calcified valves [18].

Disruption of the endothelium integrity during arteriosclerosis may establish the inflammatory cascade for atherosclerotic plaque formation. Conversely, the atherosclerotic plaque may develop early in ESRD, and calcium deposition in the atherosclerotic plaque may be accelerated [19, 20]. There is also evidence of biomarkers of bone formation in the vasculature. This may promote

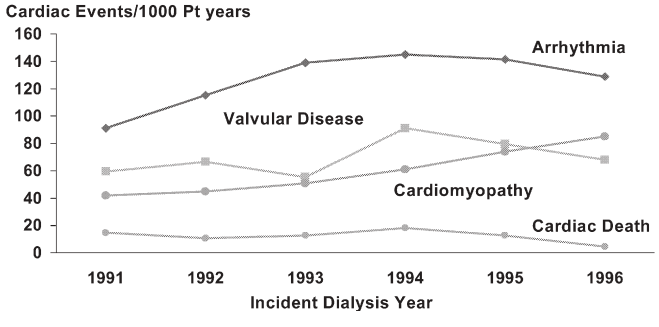

Fig. 2 Annual cardiac events per 1,000 patient years in pediatric ESRD adjusted for age, sex, race, and primary ESRD diagnosis (USRDS 1991–1996). Adapted from Ref. [13]

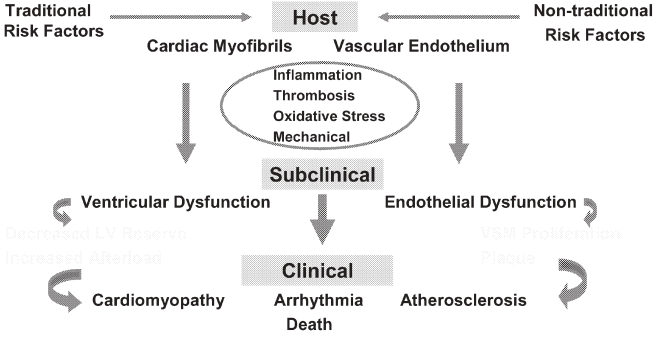

Fig. 3 Schematic diagram of cardiovascular disease in chronic kidney disease

progressive arterial wall calcification and stiffness, and worsening of both intimal and medial wall calcification [21, 22]. Increased parathyroid hormone (PTH) levels have been associated with increased coronary calcium [20] but not consistently [19], and the contribution of PTH metabolism to premature arterial calcification needs to be further elucidated.

Ventricular hypertrophy

The two most important factors contributing to the development of ventricular hypertrophy are hypertension and chronic volume overload, which are associated with chronic anemia and fluid retention. Hypertension increases ventricular afterload and causes left atrial dilation and LV hypertrophy as a compensatory mechanism (Fig. 3). Volume loading is an even more potent stimulus to the development of atrial dilation and ventricular hypertrophy. Arteriosclerosis results in stiffening of the aorta and large capacity arteries, and is a major determinant of LV pressure overload [16]. Arterial stiffening from vascular calcification has been shown to increase systemic pulse wave velocity, and afterload, which in turn impacts LV function.

There is evidence of increasing LV hypertrophy in children with chronic kidney disease (CKD) and ESRD [23]. LV hypertrophy occurs in 40%–75% of the pediatric ESRD population depending on the classification of LV hypertrophy [24, 25, 26, 27, 28]. At initiation of dialysis, 69% of subjects aged 4–18 years had evidence of LV hypertrophy [24]. Post-mortem studies have shown over 50% of children with ESRD have evidence of LV hypertrophy [18]. Chronic erythropoietin therapy has contributed significantly to the amelioration of this complication.

Cardiovascular risk factors in ESRD

Most risk factors for the development of chronic cardiovascular disease are present in a significant number of patients with ESRD. Not only are traditional cardiovascular risk factors such as hypertension and dyslipidemias present, but novel risk factors such as homocysteine and CRP are highly prevalent in the ESRD population as well.

Hypertension is seen in 49% of children with CKD [29] and 50%–60% [30] of patients on dialysis. Hypertension is more common in the transplant population, with 65%–80% of patients being treated [30]. In the young adult population, aged 18–35 years, systolic hypertension occurs in 51% and diastolic hypertension occurs in 35% of the dialysis population [31].

Lipoprotein abnormalities are increasingly recognized as complicating factors in ESRD. Approximately 29%–87% of pediatric peritoneal dialysis patients had low-density lipoprotein (LDL) >100 mg/dl (>2.29 mmol/l) [32]. Similarly, 72%–84% of pediatric kidney transplant recipients had LDL>100 mg/dl (>2.29 mmol/l) [32]. In ESRD, triglycerides are consistently elevated, with average triglyceride levels greater than 150 mg/dl, and HDL-cholesterol levels, generally thought to be protective against coronary artery disease are diminished. Lp(a), a lipoprotein associated with a mild increase in risk in the general population, is significantly elevated in ESRD, although the importance of this is unclear since it is genetically determined, and also levels are related to worsening renal function.

Two additional risk factors are much more common in ESRD than in the general population; these are homocysteine and CRP. Homocysteine has procoagulant activity and may cause direct injury to the endothelium. Homocysteine levels also increase with worsening renal function, as metabolism of homocysteine may require intrarenal metabolism [33]. Homocysteine is elevated in >65% of children with CKD [34]. Interestingly, the level only increases after 7 years of age, and this appears to be independent of renal function [34, 35]. The higher the homocysteine levels in children with CKD, the lower the vitamin B_{12} and folate levels. This suggests a role for careful assessment of nutritional deficiencies in the pediatric ESRD population [34, 35].

CRP is strongly associated with future cardiovascular events, although the magnitude of its association with risk prediction is under debate. The main reason for controversy is its strong association with conventional risk factors. Thus, it is unclear whether elevated levels represent vascular inflammation associated with a high-risk environment or are independent predictors in themselves. It is also unclear whether CRP may be most useful as a marker of acute vascular instability or a marker of ongoing chronic vascular damage. Cross-sectional measurements of CRP reveal elevated levels that are three times higher in pediatric ESRD patients on dialysis and two times higher in transplant recipients compared with healthy controls [20]. Furthermore, CRP is highly correlated with coronary calcium, especially in patients who also have an elevated PTH level. An elevated CRP level may reflect chronic inflammation from many sources, including overt or occult infectious processes, co-morbid conditions such as access complications, and factors associated with the dialysis procedure per se, including bioincompatible membrane and possibly dialysate leak in the membrane [36]. The high CRP levels in ESRD [37] are consistent with a milieu that promotes vascular injury.

Additional risk factors such as malnutrition, oxidative stress, proteinuria, anemia, infection, medications, and activation of the renin-angiotensin system have increased prevalence in CKD. In addition, in the dialysis population, calcium phosphorus metabolism with an elevated phosphorus has been associated with increased mortality [38, 39] and vascular calcification [19, 20]. In the adult CKD population, low-calcium dialysate and non-calcium-containing phosphate binders are advocated. The role of limiting calcium in growing children with ESRD needs to be addressed.

A significant difference between pediatric and adult ESRD is the frequency of diabetes mellitus as a primary

etiology. Since diabetes mellitus is a major cause of ESRD in adults, the link between diabetes and long-term cardiovascular outcome in older individuals is self evident. Pediatric ESRD patients, however, may be at high risk for insulin resistance through several mechanisms: treatment with medications that worsen insulin sensitivity (e.g., steroids, growth hormone), sedentary life style, and obesity. Future studies are needed to address this question. With the current obesity epidemic, it is possible that early renal dysfunction may emerge as a significant comorbidity in some individuals.

There is little information on the relationship between tobacco use and the presence of ESRD. In adult studies, tobacco use is well known to be associated with increased risk for mortality and cardiovascular complications.

Non-invasive assessment of cardiac end organ injury

A major technological advance in recent years is the ability to non-invasively assess the presence of cardiovascular target end organ injury in the absence of manifest cardiac disease [40]. Abnormalities have been detected in youth with extremes of traditional cardiovascular risk factors, such as hypercholesterolemia, hypertension, and obesity. These include LV hypertrophy, left atrial enlargement, presence of coronary arterial calcium, endothelial dysfunction assessed by measurement of brachial artery reactivity, and the presence of increased carotid arterial wall thickness. These markers of target organ injury have been associated with cardiovascular events in adults. The discussion above suggests that children with ESRD are at increased cardiovascular risk; studies of these non-invasive measures of end organ injury confirm this suspicion.

The most important and well-studied non-invasive diagnostic tool is echocardiography. Cardiovascular function and the presence of pericardial disease are routinely assessed and LV mass can be measured. LV hypertrophy is secondary to the chronic volume loading associated with anemia and uremia as well as hypertension. The LV mass index in the dialysis population is almost twice that of the healthy controls [23]. Frequent monitoring of the pediatric dialysis population is warranted, with a 40%–75% prevalence of LV hypertrophy despite treated hypertension [24, 25, 26, 27, 28]. LV hypertrophy, an LV mass >51 kg/$m^{2.7}$, can be treated by maintaining higher levels of hemoglobin with the use of erythropoietin [41], and by effectively treating hypertension.

One of the most striking atherosclerotic precursors in ESRD is the presence of coronary calcium on coronary computed tomography (CT) by either helical or electron beam CT. There is increased coronary calcium in young adults with a history of pediatric ESRD [19, 20]. It is unknown whether this represents a dramatic acceleration of atherosclerosis in ESRD or an increased propensity for calcium to accumulate in the medial wall of the coronary vessel due to altered calcium metabolism in ESRD. Although coronary calcium develops in the 3rd decade in patients with ESRD, recent observations in young adults that risk factors assessed years before the measurement of non-invasive target organ injury are better predictors than contemporary risk factors. This suggests that the pediatric ESRD patient with many cardiovascular risk factors is highly likely to have coronary calcium as a young adult [42].

Endothelial dysfunction assessed by brachial artery reactivity has been demonstrated in CKD. These findings are independent of lipid levels and hypertension but are correlated with LV mass index [35, 43]. This technique remains a research tool.

Risk factor management

Current guidelines for cardiovascular risk factor management in ESRD are incomplete. The presence of malignant forms of myocardial adaptation to stress such as LV hypertrophy, cardiomyopathy, and/or atherosclerosis suggests the need for aggressive treatment (Table 1).

Treatment of hypertension is well established, and includes pharmacological therapy and control of intravascular fluid management. A blood pressure less than the 90th percentile for the child's age, gender, and height, as recommended by the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents, is an appropriate goal (http://www.nhlbi.nih.gov/guidelines/hypertension/child_tbl.htm). An unresolved question in children is the level for optimal blood pressure control; should the target be lowered to the 50th percentile for appropriate age, gender, and height (analogous to the adult goal of <120/80 mmHg)?

Regression of LV hypertrophy is possible in patients on dialysis [44]. Close monitoring of blood pressure and also yearly echocardiograms to monitor cardiac size are critical to prevent LV hypertrophy. Specific medications have been recommended for preserving severe LV dysfunction; these include angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and β_1-selective blockers such as carvedilol and metoprolol. Pediatric trials are underway to support these recommendations based mostly on clinical experience and adult data [45]. Other supportive measures include fluid management with diuretics and/or dialysis. Digoxin, formerly a mainstay of congestive heart failure treatment, has more limited use in contemporary management, and may not be necessary if regulation of therapeutic levels is complicated by renal failure.

The most recent guidelines for lipid management have been developed for adults (National Cholesterol Panel-Adult Treatment Panel III). These recommendations recognize the importance of aggressive lipid-lowering therapy in patients with documented coronary artery disease or the presence of coronary artery disease equivalents such as diabetes mellitus. Current pediatric guidelines do not address the issue of accelerated cardiovascular disease

Table 1 Recommendations for assessment and management of cardiovascular risk factors in chronic kidney disease (*LDL* low-density lipoprotein, *BMI* body mass index)

Traditional risk factor	Assessment	Threshold values	Treatment goal	Comments on therapy
Blood pressure	Clinic measurement	>95th percentile for age, height, and gender	<90th percentile for age, height, and gender	Usually requires multiple medications Achieving dry weight if applicable Echocardiogram yearly
Cholesterol	Fasting lipid profile yearly in children >3–5 years of age	LDL-cholesterol ≥130 mg/dl	LDL-cholesterol <130 mg/dl	Diet modification, if unsuccessful statin therapy for LDL ≥160 mg/dl in post-pubertal children
Tobacco use	History of use in children >10 years of age	Tobacco use	Smoking cessation	Smoking cessation programs
Obesity	BMI at clinic visits	BMI≥95th percentile for age/gender	BMI<85th percentile for age/gender	Diet, exercise, weight loss programs
Family history	Early myocardial infarction/stroke less than age 50 years			Monitor cardiovascular risk factors closely

caused by diabetes or CKD [46]. A recent statement from the American Diabetes Association has attempted to update the 1992 Pediatric NCEP guidelines to reflect both increased awareness of accelerated cardiovascular disease in diabetes mellitus and new clinical experience with the HMG Co-A reductase inhibitors (statins) [47]. As all children with chronic kidney disease are at high risk, similar to children with diabetes, a recommended diagnostic and treatment algorithm would include screening and monitoring children with a fasting lipid profile. Fasting lipoprotein levels could be obtained yearly, and dietary modification initiated when appropriate in children with CKD. If children are prepubertal or less than 10 years of age, recommendations for treatment should follow the guidelines proposed by the expert panel in children [46]. Children >10 years of age or postpubertal could be considered for lipid-lowering therapy with a statin for LDL-cholesterol ≥160 mg/dl, a non-HDL-cholesterol of ≥190 mg/dl, or an LDL-cholesterol of ≥130 mg/dl if extreme risk is thought to be present. The current NKF K/DOQI guidelines on treatment of dyslipidemia should be used for children and adolescents with advanced CKD and ESRD [48, 49]. There are currently no specific treatments for elevations of Lp(a).

For other risk factors, treatment is less certain. In 25 children with CKD, a double-blind placebo-controlled randomized crossover trial of folic acid for 8 weeks showed statistically significant improvement in endothelial-dependent dilatation with lowering of homocysteine levels [50]. However, long-term effects of homocysteine lowering need to be studied to determine if improved endothelial function is sustained despite worsening kidney function. Lowering homocysteine has not yet been proven to improve cardiovascular survival in the general population. Currently, in the transplant population, a nationwide, multicenter clinical trial randomized controlled trial, The Folic Acid for Vascular Outcome Reduction in Transplantation (FAVORIT), is underway to determine whether total homocysteine-lowering treatment with a high-dose combination of folic acid, vitamin B_{12}, and vitamin B_6 reduces the rate of cardiovascular disease among 4,000 stable renal transplant recipients with mild to moderately elevated total homocysteine levels [51].

Tobacco use should be monitored, and smoking cessation programs initiated where necessary. It is probably useful to also monitor insulin resistance in high-risk individuals.

Summary

In CKD, the origins of cardiovascular mortality and morbidity are in childhood when the cardiovascular risk milieu is established. Natural history studies are underway to better document the presence of cardiovascular risk factors in CKD, and their association with cardiovascular subclinical disease. In the interim, clinicians need to consider reducing the risk of cardiovascular disease by modifying traditional cardiovascular risk factors, and monitoring for end organ injury through the use of echocardiography, and, in young adults, CT studies for coronary calcium. Chronic cardiovascular risk factor reduction, begun early in the course of CKD, is now an essential part of clinical management.

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