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Review

Chronic kidney disease and cardiac morbidity — What are the possible links?

Michael Freundlich [a,*], Steven E. Lipshultz [b], Guido Filler [c,d,e,f]

[a] Department of Pediatrics, Division of Pediatric Nephrology, University of Miami Miller School of Medicine, Miami, FL, United States
[b] Department of Pediatrics, Wayne State University School of Medicine, Children's Hospital of Michigan, Detroit, MI, United States
[c] Department of Pediatrics, Division of Pediatric Nephrology, Children's Hospital, London Health Sciences Centre, University of Western Ontario, London, Ontario, Canada
[d] Department of Pediatrics, Schulich School of Medicine & Dentistry, University of Western Ontario, London, Ontario, Canada
[e] Department of Medicine, Division of Nephrology, Schulich School of Medicine & Dentistry, University of Western Ontario, London, Ontario, Canada
[f] Department of Pathology and Laboratory Medicine, Schulich School of Medicine & Dentistry, University of Western Ontario, London, Ontario, Canada

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ABSTRACT

It is increasingly clear that the long-term outcome of children with chronic kidney disease (CKD) is associated with their cardiovascular outcomes. Renal dysfunction affects cardiovascular outcomes, and cardiovascular dysfunction affects renal outcomes. Despite many publications about cardio-renal syndrome (CRS) types I to III (acute CRS, chronic CRS and acute renocardiac syndrome), the literature about type IV CRS (chronic renocardiac syndrome) remains scant. Here, we summarize the pathophysiological risk factors of cardiovascular comorbidity and CKD. We address the exceedingly high prevalence of cardiovascular morbidity and mortality in children and adolescents with CKD and their risk factors for cardiovascular disease (CVD). Of these risk factors, uremia, renal osteodystrophy, vitamin D pathophysiology, and Fibroblast Growth Factor 23 (FGF23)-related direct effects on the myocardium and the large vessels appear to be the most prominent. We identify potential targets for intervention and highlight the need for a multidisciplinary approach involving both pediatric cardiologists and nephrologists.

1. Introduction

Chronic kidney disease (CKD) has emerged as a global healthcare epidemic that is associated with a progressive and massive increase in morbidity and mortality, mainly from cardiovascular disease (CVD) [1,2]. The rate of CVD mortality among children with end-stage renal disease in the US has increased by 32% from 1991 to 1997 and remained stable from 1997 to 2007 [2]. Mortality has been reported to be as high as 51% in European children on dialysis [3]. Cardiac death rates from maintenance dialysis are about a 1000-fold as high in children as those in the general population [4]. In contrast to non-renal patients, where most cardiac deaths result from coronary artery disease, patients with advancing CKD or on dialysis mostly die from sudden cardiac death. Cardiac arrest occurs in adults at an estimated rate of 7 arrests per 100,000 hemodialysis sessions [5]. In children with advanced CKD, arrhythmias are the most common cardiac event (19.6%) and the incidence rate of cardiomyopathy has increased from 4.2 to 8.5 cases per 100 patient-years ($P = 0.003$) [6].

Even less-severe forms of CKD are associated with marked CVD risk. In several large-scale studies (e.g., SOLVD [Studies Of Left Ventricular Dysfunction], TRACE [Trandolapril Cardiac Evaluation], SAVE [Survival And Ventricular Enlargement], and VALIANT [Valsartan in Acute Myocardial Infarction]), in which individuals with a baseline serum creatinine concentration of 2.5 mg/dL or higher were excluded, reduced renal function was associated with significantly greater mortality and adverse CV event rates [7–10]. Thus, The National Kidney Foundation and the American Heart Association now recognize CKD as an independent risk factor for CVD [11,12]. In children, elevated cardiac troponin T levels (an indicator of cardiomyocyte damage) and left ventricular contractility, both biomarkers of cardiac morbidity, correlate with markers of glomerular filtration rate (GFR) [13].

At the same time, CVD is a risk factor for progressive CKD, as a result of a complex bidirectional relationship between the heart and the kidneys through several pathophysiological pathways best exemplified by the cardiorenal and renocardiac syndromes [14,15]. Attempts to delineate these interrelated syndromes have resulted in a classification with five cardiorenal syndrome subtypes: types I and II are initiated by acute or chronic heart disease, respectively, and lead to kidney malfunction; types III and IV are acute or chronic kidney disorders, respectively, which cause or contribute to cardiac dysfunction; and type V is a systemic process (e.g., sepsis) that causes both cardiac and renal disease [16]. The present review is restricted to type IV cardiorenal syndromes (or more specifically, the chronic renocardiac syndrome) and focuses on the pathophysiological mechanisms initiated by primary

* Corresponding author. Division of Pediatric Nephrology, University of Miami, Miller School of Medicine, PO Box 016960 (M-714), Miami, FL 33101, United States. Tel.: +1 305 585 6726; fax: +1 305 585 5400.

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CKD contributing to the different alterations in cardiac structure and function that characterize the cardiomyopathy of chronic uremia.

1.1. Risk Factors of Cardiac Hypertrophy in Chronic Kidney Disease

Progressive CKD is associated with worsening CVD risk and a host of traditional and non-traditional factors capable of affecting the structure and function of the heart (Table 1). Cardiovascular risks include fatal and nonfatal myocardial outcomes, including myocardial infarction, congestive heart failure, arrhythmias, and sudden death. Leading among the intermediate surrogate markers of CVD risk are left ventricular mass (LVM), left ventricular hypertrophy (LVH), LV systolic and diastolic function, and vascular calcification.

1.2. Left Ventricular Hypertrophy

Left ventricular hypertrophy can be identified in the early stages of CKD and tends to progress with age [17]. It is associated with adverse CV outcomes in young adults treated with dialysis since childhood [18]. Ultimately, LVH and myocardial fibrosis can provoke sudden cardiac death by arrhythmia or cardiac failure, as well as contribute to the development of heart failure [19]. In a large cohort of adults in the Chronic Renal Insufficiency Cohort (CRIC) Study with established CKD assessed by cystatin C-estimated glomerular filtration rate (eGFRcys) and no known clinical heart failure, the overall prevalence of LVH was 50% and ranged from 32% in patients with eGFRcys of 60 ml/min/1.73 m^2 or higher to 75% in those with eGFRcys less than 30 mL/min/1.73 m^2. Renal function was significantly associated with abnormal left ventricular geometry across varying levels of renal dysfunction but had only minimal or no association with diastolic and systolic function [20].

The low prevalence of systolic dysfunction reported suggests that structural cardiac abnormalities (particularly increased ventricular mass and LVH) and diastolic dysfunction constitute the main precursors of heart failure in patients with CKD. In fact, LVH and elevated left ventricular mass index (LVMI) often precede various outcomes, such as congestive heart failure, cardiac ischemia, arrhythmias, and stroke [21]. Left ventricular hypertrophy is present in up to 85% of children on chronic hemodialysis [17,22,23], whereas rates of LVH of about 30% are already evident in children with much milder degrees of CKD [24–26]. Defining LVH with stricter criteria, namely, adjusting LVMI for height-age rather than to chronological age to mitigate potential effects of stature on height-based LVMI calculations, results in rates of LVH ranging from 48% to 55% [27,28].

Table 1
Traditional and chronic kidney disease-specific risk factors affecting myocardial structure and function.

Traditional risk factors	CKD-specific risk factors
Older age	Type of CKD
Hypertension	Decreased GFR
Diabetes mellitus	Proteinuria
Tobacco use	Dysregulated RAS
	ECF volume overload
Physical inactivity	Dialysis-induced volume biochemical fluctuations
Psychosocial stress	Pronounced dyslipidemia
Family history of CVD	Anemia
	Malnutrition
	Inflammation
	Infection
	Thrombogenic factors
	Elevated homocysteine
	Uremic toxins
	CKD-MBD

CKD, chronic kidney disease; CVD, cardiovascular disease; ECF, extracellular fluid; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RAS, renin–angiotensin system; CKD-MBD, CKD-mineral bone disorder.

It is important to note that LVH is multifactorial, and potentially all factors may have additive effects. The traditional "Framingham-style" risk factors (hypertension, diabetes, dyslipidemia, smoking, overweight, hypercholesterolemia, and hyperhomocystinemia) still apply. However, taking the example of hyperhomocystinemia, an effective intervention, such as folate supplementation, had no beneficial effect in CKD patients [29].

Risk factors for LVH specific to CKD include hemodynamic overload, anemia, calcium-phosphate disorders, electrolyte imbalances, chronic inflammation, oxidative stress, hypercatabolism, and uremia [30]. Risk factors specific to dialysis include intra- and inter-dialytic changes in cardiac filling (see the section on myocardial stunning, below), fluctuations in blood pressure and serum electrolyte concentrations, bioincompatibility of membranes, dialysis impurity [30], and overly ambitious attempts to achieve a "dry weight" [31].

Although several of the risk factors in Table 1, including hypertension, may contribute to LVH in advanced CKD, these factors may be less important in patients with early CKD. The ESCAPE study investigators found no relationship between ambulatory blood pressure monitoring characteristics and LVH, suggesting that hypertension appears to be a minor contributor to LVH in early CKD [32]. Similarly, observations in a smaller cohort of children with moderate CKD also showed that blood pressure did not predict LVMI [33]. However, longitudinal studies did identify a relationship between blood pressure and LVH [34].

Nontraditional risk factors, such as CKD-mineral bone disorder (CKD-MBD) may contribute to the initiation and progression of LVH [35]. The term, CKD-MBD, substitutes for the more restricted definition of renal osteodystrophy and includes a wide range of abnormalities [36]:

- Abnormal laboratory values of calcium, phosphorus, parathyroid hormone (PTH), vitamin D, and FGF23-Klotho
- Changes in bone turnover, mineralization, volume, and linear growth, and strength
- Calcification of vessels (including coronary arteries) and soft tissues.

The homeostatic control of calcium and phosphorus is complex and involves a series of feedback loops among three major hormones, PTH (synthesized in the parathyroid glands), activated vitamin D (produced by the kidneys), and fibroblast growth factor 23 (FGF23; secreted from the bone). In CKD, these homeostatic loops are disturbed and may contribute to structural and functional cardiac abnormalities in patients with CKD.

1.3. Cardiac Stunning

The cardiovascular morbidity and mortality of hemodialysis patients is particularly high [37]. Hemodialysis is an independent risk factor for the development of both *de novo* and recurrent heart failure, with a 2-year mortality after a diagnosis of congestive heart failure as high as 51% [37]. Classical complicated atherosclerotic disease does not appear to be the predominant mode of death in hemodialysis patients [38]. A substantial percentage of cardiac mortality is from sudden death, which appears to be temporally related to the dialysis procedure [39]. This observation led to the hypothesis that hemodialysis may precipitate myocardial ischemia [38]. Short and intermittent hemodialysis, especially, carries marked hemodynamic effects, and about one-third of treatments are additionally complicated by episodes of clinically important intradialytic hypotension [40].

The conventional Framingham risk factors may further influence the likelihood of myocardial ischemia, especially in older patients, but diabetic dialysis patients have a reduced coronary flow reserve in the absence of coronary vessel lesions [41]. Furthermore, patients on hemodialysis often have ventricular hypertrophy, which is associated with reduced arterial compliance [42], impaired microcirculation, and ineffective vasoregulation [38]. McIntyre et al. studied this ventricular hypertrophy extensively using electrocardiographic changes and $H_2^{15}O$