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MINI REVIEW

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Cardiovascular disease in childhood and adolescence: Lessons from children with chronic kidney disease

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Abstract

Children suffering from chronic kidney disease (CKD) have the apparent highest risk for the development of cardiovascular disease (CVD) at a young age. While symptoms of CVD are characteristically absent in childhood and adolescence, remodelling of the myocardium, medium and large-sized arteries and of the microcirculation is clinically significant and can be assessed with non-invasive technology. Kidney disease and its progression are the driver of CVD, mediated by an unparalleled accumulation of risk factors converging on several comorbid conditions including hypertension, anaemia, dyslipidaemia, disturbed mineral metabolism and chronic persistent inflammation. Large prospective paediatric cohorts studies have provided valuable insights into the pathogenesis and the progression of CKD-induced cardiovascular comorbidity and have characterised the cardiovascular phenotype in young patients. They have also provided the rationale for close monitoring of risk factors and have defined therapeutic targets. Recently discovered new biomarkers could help identify the individual risk for CVD. Prevention of CVD by aggressive therapy of modifiable risk factors is essential to enable long-term survival of young patients with CKD.

KEYWORDS

chronic kidney disease, cardiovascular disease, arterial calcification, left ventricular hypertrophy, intima-media thickness, arterial stiffness, microvascular rarefaction

1 | INTRODUCTION

1.1 | Cardiovascular mortality in children

Cardiovascular disease (CVD), a term which comprises all diseases of the circulatory system, is the leading cause of death in the world. The WHO has estimated that 17.9 million people died from CVD in 2016, representing 31% of all global deaths, of which 85% were due to heart attack and stroke. Atherosclerosis, an inflammatory disease of the large and medium-sized arteries, is the main underlying cause of CVD in the general population. Atherosclerosis develops slowly over the course of several decades, and cardiovascular events are very uncommon in children and adolescents. However, CVD is dramatically accelerated in the presence of several defined paediatric

Abbreviations: 4C, cardiovascular comorbidity in children with CKD; ABPM, ambulatory blood pressure monitoring; CKD, chronic kidney disease; CKiD, chronic kidney disease in children; CVD, cardiovascular disease; DHHD, daily home haemodialysis; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; HDF, Haemodiafiltration; NHHD, nocturnal home haemodialysis; NIHD, nocturnal intermittent haemodialysis (in-centre); RAAS, renin-angiotensin-aldosterone system; SDHD, short daily haemodialysis; suPAR, serum soluble urokinase receptor; uEGF, urinary epidermal growth factor; USRDS, United States Renal Data System.

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diseases, where clinical cardiovascular events frequently occur in childhood or very early in adult life, that is before the age of 30. These include homozygous familial hypercholesterolaemia, type 1 diabetes mellitus, heart transplantation, and Kawasaki disease with coronary aneurysms and chronic kidney disease (CKD).[1] By widely accepted definition, criteria for CKD are the presence of markers of kidney damage or a glomerular filtration rate (GFR) <60 mL/min per 1.73 m^2 for >3 months. About 20 years ago, retrospective studies in Europe found that children with CKD are the paediatric population with the highest cardiovascular risk.[2,3] This was confirmed and most clearly illustrated by data from the United States Renal Data System (USRDS) collected in 2006-2008 for children aged 0-19 years with end-stage kidney disease, showing mortality rates of 35.6 (dialysis) and 3.5 (transplant) per 1000 patient-years.[4] For comparison, overall mortality rates were 0.31 per 1000 population for children aged 1-19 years in 2008 in the general US paediatric population.[5] Earlier USRDS data for adults (1994-1996) had shown that annual mortality from CVD was much higher in dialysis patients compared to the general population and elevated almost 1000-fold in the age group of 25-34 years.[6] A more recent similar analysis (USRDS, 2003-2013) in young patients with incident CKD found an incremental increase in mortality from early childhood to young adulthood (age groups 1-11, 12-21, 22-29) and concluded that young adults with incident ESRD had a 143 to 500 times higher risk for CVD, and that CVD accounted for almost 40% of the total mortality.[7] Hence, CKD has been acknowledged as a strong and independent risk factor for CVD; patients with CKD should be considered in the highest risk group for cardiovascular events.[8] Today, in spite of decades of progress in medical management of CKD including technical advances in dialysis and transplantation therapy, CVD is the strongest impediment for long-time survival of young patients with CKD.

Key Notes

- Children suffering from chronic kidney disease (CKD) have the highest risk for the development of cardiovascular disease at a young age.
- CKD induces clinically silent, but progressive remodelling of the myocardium, medium and large-sized arteries and the microcirculation, which can be assessed with non-invasive technology.
- Aggressive therapy of modifiable risk factors and augmentation of dialysis treatment is essential to enable long-term survival of young patients with CKD.

2 | RISK FACTORS

Epidemiological studies have revealed that CKD is fraught with an unparalleled accumulation of risk factors for CVD, including traditional (such as hypertension, hyperlipidemia) and non-traditional (uraemia-related) risk factors. These risk factors were originally defined by association studies with hard end-points of cardiovascular disease (myocardial infarction, stroke, arrythmia, death) observed in adults in the general population. The infrequent occurrence of such events during childhood necessitated the development of non-invasive methods to measure surrogate parameters reflecting early pathological changes of the cardiovascular system. Even small increments of these parameters are highly predictive of future cardiovascular events in the general population and in adults with CKD.[9] Population-based studies in children have established age-related normal values for defined surrogate parameters including the left ventricular mass index, the carotid artery intima-media thickness, and pulse wave velocity.[10-12] Measurements above the 95th percentile for age have been defined as intermediate end-points for CVD. Ultrasound technology also permits measurement of local arterial stiffness of the common carotid artery with M-mode sonography (increased in CKD) and flow-mediated dilation of the brachial artery (diminished in CKD) to assess endothelial dysfunction; however, no age-related normal values have been established for these techniques.

Several cross-sectional studies, usually investigating children with various stages of CKD including dialysis, have detected a remarkably similar assembly of risk factors associated with surrogate measurements. These include hypertension, dyslipidaemia, disturbances of mineral metabolism and treatment with active vitamin D preparations, anaemia, and in dialysis patients, the duration of dialysis treatment.[13]

3 | PROSPECTIVE STUDIES IN PAEDIATRIC CKD PATIENTS

During the last decade, large prospective paediatric cohort studies have contributed significantly to our understanding of progression or CKD and the relative impact of risk factors on the cardiovascular system. The Chronic Kidney Disease in Children (CKiD) study was started in 2006 with 540 American children aged 1-16 years (baseline eGFR 30-75 mL/min per 1.73 m^2) to study the impact of kidney function decline on growth, cognition, and behaviour and the evolution of cardiovascular disease risk factors (Furth, Cole et al 2006). The Cardiovascular Comorbidity in Children with CKD (4C) was started in 2009 and could enrol >700 European children with a baseline estimated glomerular filtration rate (eGFR) of 10-60 mL/min per 1.73 m^2; progression of cardiovascular comorbidity as well as its association with CKD progression has been prospectively recorded by twice annual follow-up including measurements of surrogate parameters for CVD.[14] Confirming previous single centre cross-sectional data, these studies found a high prevalence of abnormal surrogate parameters with an incremental increase with advancing stages of CKD, suggesting that cardiovascular remodelling already starts at an early stage of CKD and that progression of CVD parallels the loss of renal function. In the 4C study, the intermediate end point score (derived from the number of surrogate marker measurements >95th percentile) at study entry was independently associated

with a diagnosis of congenital anomalies of the kidney and urinary tract, time since diagnosis of CKD, body mass index, office systolic blood pressure, the serum phosphorus level and the haemoglobin concentration.

4 | THE PHENOTYPE OF CVD IN CKD

The baseline data from the 4C study showed that the prevalence of left ventricular hypertrophy was higher with each CKD stage (10.6% in CKD stage 3a to 48% in CKD stage 5). The carotid intima-media thickness was elevated in 41.6%, and only 10.8% of patients had measurements below the 50th percentile. Pulse wave velocity was increased in 20.1%.[15] These data and similar results from the CKiD study[16] have clearly demonstrated extensive myocardial and vascular remodelling and arterial stiffening in the absence of clinical symptoms.

Cardiac disease in patients with CKD is not confined to left ventricular hypertrophy. Children on dialysis have altered cardiac mechanics as shown by cardiac strain analysis[17] and ventricular dyssynchrony[18]; they may exhibit myocardial stunning within myocardial segments upon fluid removal fluid removal by haemodialysis, predisposing to clinically significant demand myocardial ischaemia.[19]

While these alterations in cardiac and vascular morphology and function can be considered as an early phenotype, more advanced damage to the cardiovascular system is found in patients with arterial calcifications. Widespread arterial and tissue calcifications in young dialysis patients were first reported in an autopsy study in 1990,[20] and the frequent presence of vascular calcifications in adult and paediatric patients was later confirmed in several studies using computerised scanning methods for coronary artery calcification. While these studies showed a variable prevalence of coronary artery calcifications, their burden seems to increase with time on dialysis.[13] Calcifications may also occur in cardiac valves, peripheral arteries or in soft tissues. Arterial calcifications are typically located in the arterial media, they result from an active, regulated process of transition of vascular smooth muscle cells to a chondro-osteoblast phenotype resembling bone formation, and are mainly mediated by the complex disturbances of mineral metabolism in CKD.[21] In adults with CKD, the presence of coronary artery calcifications is strongly associated with the risk of subsequent cardiovascular disease, myocardial infarction, heart failure and all-cause mortality.[22]

Finally, CKD even at early stages associates with a systemic microvascular disease.[23] Rarefaction, that is, a reduced microvascular density, has been demonstrated in uraemic patients including children[24] and in animal models of uraemia.[25] Microvascular disease is characterised by endothelial dysfunction and tissue hypoxia and may significantly contribute to the multitude of clinical comorbidities of CKD, including myocardial demand ischaemia, reduced cerebral perfusion, muscle wasting with reduced exercise capacity and fitness, further progression of CKD and more.[23] Figure 1 summarises the

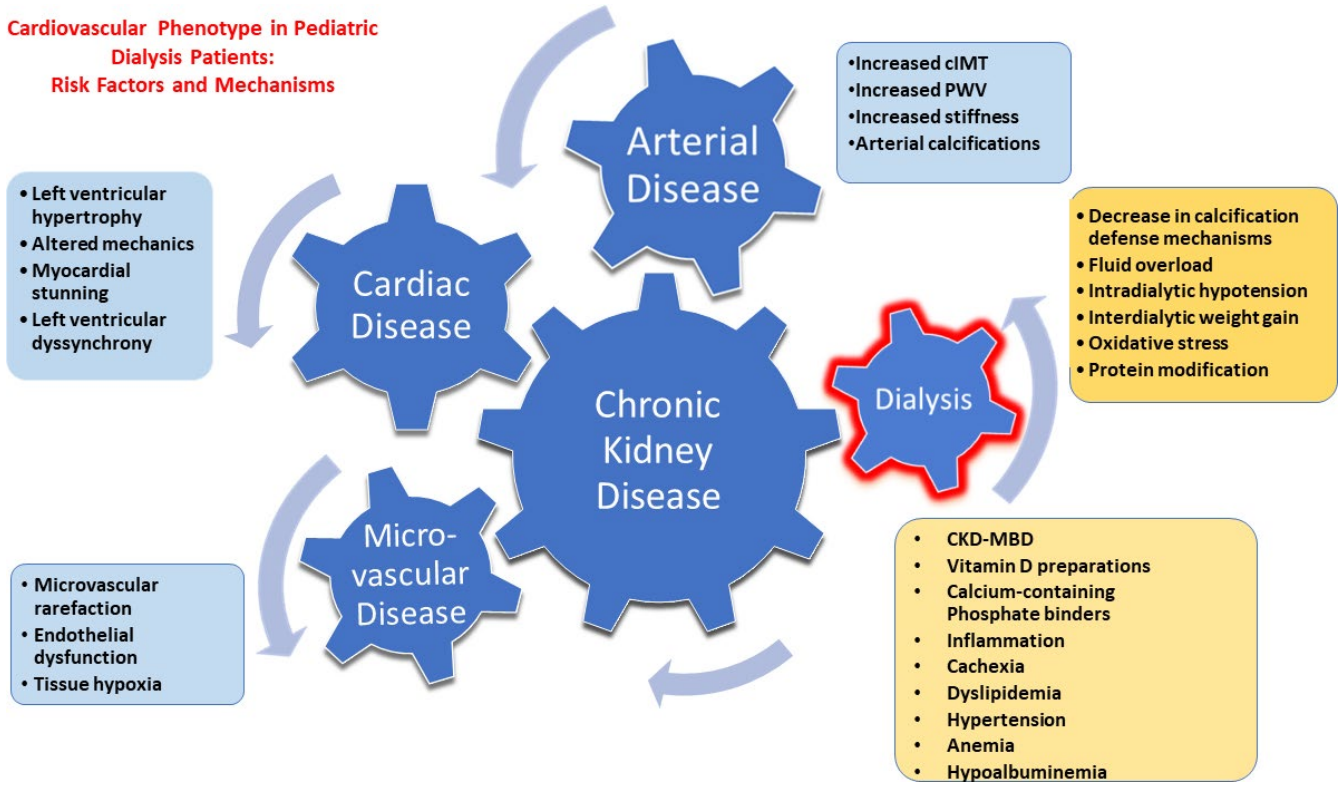

FIGURE 1 CKD related risk factors (light yellow) are associated with a silent cardiovascular phenotype (light blue) and drive cardiovascular disease by deleterious effects on the heart, arteries and the microcirculation (dark blue cogwheels); this is further aggravated by risk factors and complications (dark yellow) of dialysis treatment

features of the cardiovascular phenotype in paediatric CKD patients, their main risk factors and pathophysiological mechanisms.

5 | LESSONS LEARNED FROM CHILDREN WITH CKD

5.1 | Calcifying arteriopathy

The extremely high amount of calcium in coronary arteries of some young subjects with CKD is highly unusual in view of the natural history of atherosclerosis. In the general population, autopsy studies of young victims of accidents (under the age of 40) have shown that calcium deposits emerge as granules of microscopic size in advanced lesions of atherosclerosis (type IV) in a minority of these subjects; advanced lesions containing large amounts of calcium do not appear until the 5th decade of life.[26] Indeed, vascular changes in young patients with CKD differ from atherosclerosis. Imaging and biopsy studies have revealed increased calcium content and stiffening of arteries in early stages of CKD and in-situ calcifications mainly in dialysis patients, but no evidence for atheroma formation.[21,27,28] Children with predialysis CKD show early changes in arterial gene transcription consistent with calcium accumulation, matrix remodelling, increased stiffness and premature ageing.[28] Thus, young patients with CKD may rapidly develop arteriosclerosis with media calcifications, while additional atherosclerotic lesions (often with intima calcifications) are seen in adult CKD patients.[29]

5.2 | Overall importance of blood pressure control

The office systolic blood pressure (expressed as standard deviation or z-score) was the single independent factor significantly associated with all surrogate markers of cardiovascular disease in the 4C study at baseline. This suggests a strong and dose-dependent effect of blood pressure on remodelling of the cardiovascular system. Blood pressure was further evaluated by ambulatory blood pressure monitoring (ABPM) in 545 patients participating in this study. Using the 95th percentile of 24-hour mean arterial pressure[30] as the diagnostic criterion, 26.1% of patients were hypertensive. Masked hypertension was found in 14.5% and white coat hypertension in 11.2%. The majority of patients received antihypertensive therapy (33%, one drug; 24.2%, two drugs; and 17.2%, three or more drugs); nevertheless, hypertension was uncontrolled in 28.6%. These data show that evidence-based blood pressure targets are not met in clinical practice. Similar findings have been reported in other studies, indicating that a considerable percentage of children with CKD has either undiagnosed or undertreated hypertension.[16]

Hypertension is a modifiable risk factor, and a significant improvement in blood pressure control seems all important to prevent target organ damage in children with CKD of all stages, including patients after kidney transplantation. ABPM is an indispensable tool in the diagnosis and management of paediatric hypertension.[31] The value of ABPM-based blood pressure control has been confirmed in a single-centre study of paediatric kidney transplant recipients, who had no increase in carotid intima-media thickness and a low prevalence of left ventricular hypertrophy with controlled hypertension during follow-up of 9 years.[32] Inhibitors of the renin-angiotensin-aldosterone system (RAAS) are used as first-line drugs in the pharmacological treatment of children with CKD. They have antihypertensive and antiproteinuric effects and slow the progression of CKD,[30] but are sometimes discontinued during the progression of CKD. However, as shown by a recent analysis of patients participating in the 4C study, discontinuation was associated with increases in blood pressure and albuminuria and an accelerated eGFR decline.[33] Thus, RAAS inhibitors appear to be effective in preserving renal function even in advanced CKD.

5.3 | Many risk factors are modifiable risk factors

Studies in children using surrogate measurements of CVD such as the carotid intima-media thickness, left ventricular mass index and pulse wave velocity have the potential to identify cardiovascular risk factors (with special relevance for children) by determining the significance of association with these measurements. Again, large prospective cohort studies are most useful in this regard and have revealed several significant associations with modifiable risk factors (among other non-modifiable variables such as age). The analysis of baseline cross-sectional data of the 4C study could show significant associations of one or more of these parameters with the modifiable risk factors systolic blood pressure, physical activity, body mass index, and serum levels of parathormone, 25-OH-Vitamin D and haemoglobin. The CKiD study data show a significant association of adiposity with the left ventricular mass index and cardiovascular risk markers in American children[34,35]; in adolescents, this was independently associated with greater screen time.[36] These data are important for defining therapeutic targets to improve the treatment of children with CKD. They provide a rationale for not only aggressive treatment of hypertension, but also for behavioural modification (increase in physical activity, weight loss in obese patients, reduction of screen time) and intensified pharmacological therapy (erythropoietin, vitamin D preparations).

5.4 | CKD patients suffer from a wide range of comorbidities

Perhaps more than any other chronic disease, CKD is frequently accompanied by multiple comorbidities. These include syndromal conditions, congenital abnormalities (ocular, cerebral, auditive, limb malformations, and more) and acquired comorbidities induced by CKD. The baseline data of the 4C study showed that 6.5% of patients had defined syndromes, and 35.9% had at least one congenital comorbidity.[15] The CKiD study has given a thematic priority to the study of neurocognitive disturbances. Neurocognitive dysfunction was found in a substantial percentage of participating children[37]; a

high blood pressure[38] and a history of stroke[39] were found associated with decreased neurocognitive test performance. A systematic review found a mild cognitive deficit in children with CKD, whereas other chronic childhood illnesses—haemophilia A and cystic fibrosis—had no significant impact on cognitive development.[40] In adults, cognitive impairment was associated with retinal microvascular disease in several CKD cohort studies (reviewed in[41]), suggesting an important contribution of microvascular disease in the pathogenesis.

5.5 | Progression of kidney disease drives cardiovascular comorbidity

Altogether, progression of CKD drives cardiovascular comorbidity by deleterious effects on the heart, arteries and the microcirculation, and this is further aggravated by dialysis (Figure 1). Recent studies have provided new insights into mechanisms contributing to progression of CKD. Not surprisingly, progression is strongly influenced by the level of proteinuria and therefore faster in children with glomerular diseases compared to other causes of CKD.[42] However, paediatric cohort studies have revealed associations with neglected or previously unknown risk factors. Thus, hyperuricaemia was found to be an independent risk factor for faster progression.[43] Also, the 4C and the CKiD study could both show a significant association of CKD progression with metabolic acidosis.[44,45] This indicates that metabolic acidosis, which seems to confer damage via hormonal alterations and the complement pathway, is not merely a biochemical abnormality accompanying CKD, but should be considered as a modifiable risk factor for progression.[46] In addition, low urine concentrations of the urinary epidermal growth factor (uEGF) and elevated serum concentrations of the serum soluble urokinase receptor (suPAR), respectively, are significantly correlated to CKD progression.[47,48] The levels of uEGF and suPAR may be useful to predict CKD progression in children with CKD, and there is increasing evidence for a pathogenetic role of these biomarkers.[49,50] Similarly, gut-derived uraemic toxins such as indoxylsulphate seem to contribute to progression of CKD. Indoxylsulphate serum levels at baseline were closely correlated to kidney function and the cardiovascular phenotype[51] and to further progression of CKD in the 4C study (manuscript submitted). The evolution of the cardiovascular phenotype (as assessed by surrogate markers such as LVMI) with progression of CKD is currently under investigation and will contribute further to the understanding of the special risk for CVD in young patients with CKD. The methodology and results of these cohort studies in CKD patients may contribute to progress in the prevention of CVD in the general population.

5.6 | Dialysis aggravates the cardiovascular risk

CKD is a relentlessly progressive disease with the need for kidney replacement therapy with dialysis or transplantation when GFR is <15 mL/min/1.73 m^2. Unfortunately, registry data as well as many single centre studies have shown that treatment with haemodialysis or peritoneal dialysis aggravates pre-existing risk factors and accelerates the progression of CVD with additional dialysis-related risk factors (Figure 1), such as salt and fluid overload, intradialytic hypotension, impaired cardiac mechanics, oxidative stress and protein modification. Vascular calcifications were shown to increase with time on dialysis.[13] To overcome the limitations of conventional haemodialysis, various paediatric centres have developed intensified haemodialysis programs in the form of short daily (SDHD), nocturnal intermittent (NIHD, in centre), daily home (DHHD) or daily nocturnal home HD (NHHD). The experience with these programmes has shown that patients with any form of intensified dialysis were free of fluid or dietary restriction and that medications could be reduced and control of blood pressure, phosphate levels and anaemia was improved.[13] However, intensified dialysis regimens require changes in hospital logistics and investments in medical staff and have not been widely implemented.[52] Haemodiafiltration (HDF), a modification of the standard haemodialysis technique, can be performed in haemodialysis units without major logistical changes if suitable machines and ultra-pure dialysis fluid are available. A recent European prospective observational cohort study, the HDF, Heart and Height study, has shown that in contrast to conventional haemodialysis, HDF was associated with lack of progression of vascular measures as well as improved growth, blood pressure control and patient well-being.[53] These very favourable results of treatment with HDF, if confirmed in a randomised controlled study, hold promise for a more efficient and better tolerated form kidney replacement therapy in the future.

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CONFLICT OF INTEREST

No conflict of interest.

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