Cardiovascular risks in chronic kidney disease pediatric patients (Review)

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Abstract. One of the common factors for the premature death in children is advanced chronic kidney disease (CKD). Most often cardiovascular disease (CVD) is the reason for mortality. The cardiovascular (CV) morbidity starts early in the disease process and renal transplanted children (CKD-T) are also at risk. The present review is focused on the current views of the cardiovascular risks during CKD in pediatric patients. Variable data sources for the latest literature collection were explored which mainly included PubMed and Google Scholar. The most important risk factors for subclinical CVD were a young age, elevated BMI and systolic blood pressure z-scores as well as a low GFR and present albuminuria. Increasing blood pressure and BMI over follow-up were also important cardiac risk factors longitudinally. The present review concludes that altered cardiac function and remodeling are a concurrent part of the CKD process, start early in the disease development, and persist after renal transplantation. The findings suggest that children with CKD or CKD-T are at high risk for future CVD where younger patients with elevated BMI and slightly increased blood pressures, as well as present albuminuria, are those at greatest risk, thus indicating targets for future interventions.

Contents

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1. Introduction

An irreversible damage to kidneys that usually result in end stage renal disease (ESRD) is termed as chronic kidney disease (CKD) (1). The renal replacement therapy is the need of the hour as CKD affected patients are on continuous rise (2). These therapeutic options include dialysis or renal transplantation1. Renal transplantation improves both morbidity and survival rates, but the risks for disease and early death still remain higher than in the general age-matched population (3). CKD affected pediatric patients are less in comparison to adults but the prevalence of RRT in children has increased in the last decades. A total number of 9,921 children with RRT in the US in 2013 and 3,595 children aged 0-14 years with RRT in Europe in 2011, indicates that this is a significant medical problem (4).

The first pediatric renal transplant was performed over 50 years ago, and there have been significant improvements in post-transplant survival and care since then. In addition, advances in surgical techniques have allowed successful transplantations to be performed in smaller (and younger) children. However, mortality rates are still high, with a major cause being attributed to cardiovascular disease (CVD) (5). In the last decade new echocardiographic techniques have enabled the analysis of subtle subclinical changes in cardiac geometry and function, shown to predict future CV events and death in both the general population and adult CKD patients (6). However, long-term studies of subclinical CV morbidity in pediatric CKD are scarce.

2. Epidemiology of CKD

CKD is in simple words an irreversible loss of kidney function over time. The main causes of CKD in adults are hypertension and diabetes, constituting two-thirds of all cases. In pediatric patients, the etiology is very different from that in adults (7). The pediatric nephrology registry from North America (NAPRTCS) includes more than 7,000 children and adolescents registered between 1994 and 2008. According to this registry, 58% of pediatric CKD cases are due to congenital causes, divided into congenital abnormalities of the kidney and urinary tract (CAKUT: 48%) and hereditary nephropathies (10%). Glomerulonephritis accounted for 14%, cystic kidney disease 5% and Hemolytic Uremic Syndrome (HUS) together with ischemic renal failure composed 4% (8). In two large

European registries from Italy and Belgium, similar distributions are reported (9,10).

Regarding the cause of CKD in pediatric patients with RRT, the same trends are observed in the ESPN/ERA-EDTA registry (4). This is a European registry formed in 2007 that includes 37 countries and children with RRT aged 0-14 years. For nine of the countries, data on ages 0-19 years are also available. In their latest study, CAKUT was the dominant cause (41%) of pediatric RRT in Europe. The second largest cause was glomerulonephritis (15%), followed by cystic kidney disease (10%) and hereditary nephropathies (7%).

3. Epidemiology of CVD in CKD

In adults with RRT, arrhythmias and cardiac arrest was the most common cause of mortality, constituting 37% of all deaths according to the last report from USRDS (11). Atherosclerotic heart disease composed the majority of all CVD in patients over the age of 44 years, while in-patient aged 22-44 years, congestive heart failure was mainly responsible for CKD. In patients aged 0-21 years, congestive heart failure constituted 19% of all CVD, followed by peripheral arterial disease (17%). In contrast to the aged population with RRT, this young cohort rarely demonstrated atherosclerotic heart disease (<4%). In a large population based cohort study, Go *et al* examined more than 1.1 million adults, and identified a gradual increase in hazard ratios for adverse CV events as renal function decreased (12). Based on these observations pediatric CKD patients are put in the highest risk category (13).

4. Risk factors and risk markers

The risk factors are characteristics that could be measured in order to estimate well-defined outcomes. On the other hand, risk markers are biological indicators of disease development. Even though the causality of the following CV risk factors in CKD listed below is not fully established, they are often classified as just traditional or non-traditional CV risk factors. Non-traditional risk factors are, in the CKD population, often referred to as uremia-related risk factors. In 2011, the Chronic Kidney Disease in Children (CKiD) study, an observational cohort study of 586 children aged 1-16 years with CKD stages 2-4, published comprehensive data on CV risk factors. Overall, 39% of participants had at least one risk factor, 22% had two risk factors and 13% had three present risk factors (14). The number of prevalent risk factors increases as CKD progresses, and is highest in children on maintenance dialysis. Following kidney transplantation the prevalence of these traditional risk factors remains high. However, Kaidar *et al* recently showed that in 77 renal transplant patients the number of risk factors present decreased progressively following renal transplantation to the last follow-up visit (on average seven years) (15).

Hypertension and CKD. Hypertension in pediatric CKD results from volume expansion and increased vascular resistance, which develops as renal function deteriorates. Controlled hypertension is defined as the need of antihypertensive medications in order to regulate blood pressure levels to <95th percentile. Hypertension is confirmed risk factor for CVD (16). In children with CKD, hypertension is associated with deterioration in renal, cardiac and vascular functions (17-19). In data from the CKD cohort, 21% were normotensive, 37% had elevated blood pressure and 42% had controlled hypertension (20). In the same cohort, 14% and had uncontrolled systolic hypertension and 13% uncontrolled diastolic hypertension using office blood pressures (21). High BMI and elevated levels of proteinuria were important risk factors for a longitudinally increasing blood pressure. Equally, ambulatory blood pressure (ABP) measurements revealed that 19% had masked hypertension and 13% confirmed hypertension. Further, a high variability in mean systolic ABP was seen, but also in night diastolic ABP in hypertensive children (22).

The prevalence of hypertension increased in the immediate and short-term following renal transplantation and was 52% two months after transplantation, and decreased to 27.5% after six months, and 22% two years after transplantation (15). At the same time points, 54.8, 38 and 37.7% of patients were treated with antihypertensive medication. In another study, 27.9% of children were normotensive six months after renal transplantation and not treated with antihypertensive drugs. Of these non-hypertensive patient post-transplants, 49.3% became hypertensive and commenced antihypertensive medication during the follow-up of two years (23). Still, long-term prevalence of uncontrolled hypertension 7-18 years after renal transplantation was only 12-14% (24).

Dyslipidemia and CKD. Dyslipidemia in CKD is characterized by increased levels of plasma triglycerides (TG) and triglyceride-rich lipoproteins, as well as decreased high density lipoprotein cholesterol (HDL) and apolipoprotein A. Chylomicron remnants and VLDL accumulate in CKD patients due to increased production and impaired catabolism (25). The KDIGO recently published guidelines with cut-offs for acceptable, borderline high and high levels for cholesterol, LDL and non-LDL in children (26). The potential impact of dyslipidemia on CVD in the general population is profound. Indeed, elevated lipid levels in children without renal disease present a risk factor for later CVD (27). However, the relative risk of CVD from dyslipidemia in children with CKD compared to the general pediatric population is not known.

The dyslipidemia with CKD is commonly observed in children. Dyslipidemia is more common and severe in patients with glomerular disease and proteinuria, as well as in late stage CKD (28). Specifically, elevated levels of triglycerides and non-HDL, as well as the use of lipid lowering drugs, have been reported in 44% of children with CKD stages 2-4. As GFR declines, both triglyceride and cholesterol levels increase (29). The hypercholesterolemia frequency is high in pediatric renal transplant patients (30). After seven years the prevalence was 33 and 13%, respectively. The major cause of dyslipidemia in this patient group is not only progressive loss in renal function, but can also be attributed to medications used; particularly corticosteroids, cyclosporine and sirolimus (31).

Abnormal glucose metabolism. In CKD, glucose intolerance is primarily a result of impaired tissue sensitivity to insulin with several possible causes discussed in the literature (32). Glucose intolerance involves impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and diabetes mellitus. The American Diabetes Association (ADA) and WHO use different

definitions of these abnormalities, which generates confusion when comparing studies. The cut-off for glucose to define IFG ranges from 5.6 (ADA) to 6.1 (WHO) mmol/l (33). While other measures of insulin resistance (intravenous glucose tolerance test and glucose clamp technique) are more robust, they are invasive and usually not possible to perform in routine clinical check-ups. Alterations in glucose and insulin metabolism are important contributors of CVD and might also be of importance in adult CKD and CKD-T patients. For example, 'new-onset diabetes after kidney transplantation' (NODAT) is associated with impaired renal survival and an increased CV morbidity and mortality in adult patients (34). Very few data are available for the impact of abnormal glucose metabolism in pediatric CKD.

IGF, IGT and CKD. IFG and IGT are common in pediatric CKD, including dialysis patients. Using the ADA definitions, 35% of pediatric non-dialysis CKD patients exhibit either IFG or IGT (35). While the prevalence for hyperinsulinemia varies between studies of pediatric CKD stage 2-4 (9-33%), insulin resistance reveals similar prevalence (16-19%) (36). Moreover, using the WHO definition for IFG, overall 21% of pediatric patients in the CKiD cohort had abnormal glucose metabolism defined as IFG, hyperinsulinemia or insulin resistance.

Anemia and CKD. Anemia in CKD is predominantly caused by erythropoietin deficiency, but other factors such as acidosis, inflammation and malnutrition related to uremia contribute as well (37). Due to various definitions of anemia used historically (38), comparisons between studies have sometimes been troublesome. Following guidelines recently presented by KDIGO with cut-offs to define anemia in children at different ages, this issue is hopefully transient (39). Further, in pediatric CKD-T patients lower hemoglobin was associated with increased risk of death, and also graft loss (40). Anemia is present during early stages of CKD and is often poorly controlled, especially in children with advanced CKD35. Moreover, anemia sometimes remains after renal transplantation. Thus, 30% of pediatric patients at two months after transplantation and 18% after seven years are anemic. In a very recent large multicenter study, the prevalence of anemia, ranged from 7.8 to 49.8% depending on the cut-off used. When the definitions of anemia encompassed erythropoietin treatment, the prevalence increased to 16.3 and 58.1%. Hemoglobin levels were associated with pre-transplant care (pre-emptive transplantation vs. previous dialysis treatment), graft function and antihypertensive and immunosuppressive medications.

Chronic inflammation and CKD. The chronic inflammation is often seen associated with CKD and RRT. There is an inverse correlation between GFR and level of inflammatory cytokines as well as a positive correlation between albuminuria and inflammation (41). Different biomarkers of inflammation appear to have varying predictive values. For example, Interleukin-6 (IL-6) predicts all-cause and CV mortality more accurately than C-reactive protein (CRP) and other cytokines (42). The postulated mechanism of inflammation in CVD is that chronic inflammation promotes vascular calcification and endothelial dysfunction (43). While chronic inflammation is present in pediatric CKD and dialysis patients (42), its role in this group

remains conflicting (43). Inflammation is also discussed as a potential CV risk factor in pediatric CKD-T patients, but very few studies are available (44). The significance of inflammation in this group, receiving a variety of immunosuppressive agents is difficult to interpret.

Albuminuria and CKD. Albuminuria means excessive loss of albumin in the urine due to abnormalities in kidney functions. The presence of persistent albuminuria is an early sign of renal damage and is closely related to the progression of CKD in children (45). As for several other CV risk factors mentioned previously, comparing studies on albuminuria and proteinuria is troublesome as they often use different definitions. Microalbuminuria is often defined as spot sample urinary albumin of 30-300 mg/l and above this limit is macro-albuminuria. In addition to its role as a marker for CKD risk, it is now widely accepted that albuminuria is an independent predictor of CV morbidity and mortality across various populations (46). The pathophysiological link between albuminuria and CVD are related especially in relation to endothelial dysfunction (47).

Albuminuria is common in pediatric CKD and in the CKiD cohort, 71% had an elevated urinary protein to creatinine ratio. Approximately 20% of these patients had nephrotic range proteinuria. Longitudinal pediatric studies have shown that albuminuria is an independent predictor for CKD progression and increasing blood pressures (48). The rate of albuminuria usually falls after transplantation, and persistence or late appearance of albuminuria represents graft injury with the mechanism being multifactorial (49). In a small study of 53 renal transplanted children, 47% had pathologic urinary protein to creatinine ratio (50).

Abnormal mineral metabolism and CKD. In mineral metabolism there is a complex interaction between the kidneys, the parathyroid gland, the gastrointestinal tract, and the skeleton. In children with CKD, these mechanisms are often disrupted. Phosphorus retention begins during the earliest stages of CKD is also linked with the development of hyperparathyroidism. Ongoing research has identified other factors of importance in the regulation of phosphorus balance; Fibroblast growth factor 23 (FGF23) with Klotho reduce the expression of sodium phosphate co-transporters (NaPi2a/c) in the proximal renal tubule in the kidney to induce phosphaturia, similar to PTH. In more advanced stages of CKD, this adaptation becomes less successful, and as a result hyperphosphatemia is more commonly found (51). The role of CKD-MBD on mortality is not fully clear. Low levels of 25-vitamin D are associated with all-cause and CV mortality in adult hemodialysis patients (52), and are associated with worsened cardiac morbidity and progressive renal failure in pediatric CKD (53). However, recent meta-analyses have not been able to prove that vitamin D supplementation affect mortality or CV risk in adult CKD patients, with or without RRT (54). Further, while hyperphosphatemia also has been independently associated with mortality in adult CKD, it is clear that FGF23 increases as CKD progresses, and becomes maladaptive and possibly contributes to cardiac remodeling independent of phosphate levels (55). In addition, while FGF23 increase, Klotho decrease as the renal function deteriorates (56). Low levels of soluble Klotho has been found

to be involved in vascular calcification in CKD and other populations, but has not been linked to increased mortality (57). However, the numbers of studies are few.

Abnormal mineral metabolism is often observed in pediatric CKD patients. Although children with early stage CKD generally have no signs or symptoms of bone abnormalities, laboratory testing might already show decreased 25-vitamin D and elevated PTH (58). Current treatments focus on suppression of PTH with vitamin D supplementations. Subtle signs of bone osteodystrophy may begin in CKD stage 3 with muscle pain, weakness and bone deformations. In a small report of pediatric CKD, bone biopsy demonstrated increased bone turnover in 0, 13 and 29% and defective mineralization in 29, 42 and 79% in CKD stage 2, 3 and 4/5 (before dialysis) respectively (59). FGF23 levels increase as CKD progresses from stage 1 to 5 in children with the most marked elevation in advanced CKD (60). FGF23 is elevated also in CKD-T children (61), in which hyperparathyroidism is also common (32% two months after transplantation and 18% after seven years). Levels of soluble Klotho in pediatric CKD-T have only been published in very few previous studies (61,62).

5. Conclusions

The present review concludes that altered cardiac function and remodeling are a concurrent part of the CKD process, start early in the disease development, and persist after renal transplantation.

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