Risk Factors for the Progression of Chronic Kidney Disease in Children

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Chronic kidney disease (CKD) in children is associated with various complications, including poor growth and development, mineral bone disorder, cardiovascular disease, kidney failure, and mortality. Slowing down the progression of CKD is important since CKD is often not curable. Prospective cohort studies have been conducted to understand the progression and outcomes of CKD in children, and these studies have identified non-modifiable and modifiable risk factors. Recognition of known risk factors and early intervention are important to delay the progression of kidney function decline in children.

Key words: Chronic kidney disease, Risk factors, Children, Kidney failure

Introduction

Chronic kidney disease (CKD) is a growing public health problem worldwide with increasing incidence and prevalence¹⁾. The prevalence of CKD in children is much lower than that in adults, ranging from 15 to 75 cases per 1 million children²⁾. CKD in children, as well as in adults, is associated with serious consequences, including increased risk of mortality, kidney failure, cardiovascular disease, mineral bone disorder, and poor nutrition. Moreover, children have a longer life expectancy with a longer time to manifest complications related with CKD. Comorbidities of CKD may also lead to complications that include impairments in physical and psychosocial development in children^{3,4)}. Therefore, pediatric CKD requires a higher cost of care per individual than that in adult CKD⁵⁾.

Slowing down the progression of kidney function decline in children with CKD is important since CKD with declined renal function (estimated glomerular filtration rate (eGFR) ≤ 60 mL/min/1.73 m² body surface area for more than 3 months) has no cure. Identifying risk factors for the progression of CKD may help clinicians recognize the risk factors earlier and initiate preventive interventions for CKD and its attendant comorbidities, as well as monitor for complications. Prospective cohort studies have been conducted to understand CKD progression and outcomes in children. These studies included Chronic Kidney Disease in Children (CKiD) in North America⁶⁾, Cardiovascular Comorbidity in Children with Chronic Kidney Disease (4C) in European countries⁷⁾, and KoreaN cohort study for Outcome in patients With Pediatric Chronic Kidney Disease (KNOW-PedCKD) in Korea⁸⁾ (Table 1).

In this review, the factors that affect the progression of pediatric CKD, which were reported by previous studies, will be reviewed.

Non-modifiable risk factors

1. Primary kidney disease

Primary kidney disease is an important predictor of CKD progression in children. Congenital anomalies of the kidney and urinary tract (CAKUT) are the most common cause of pediatric CKD. Children with CAKUT experience a slower progression of CKD than those with other causes, resulting in a lower proportion of CAKUT in the population of children with kidney failure²⁾. The kidney survival analysis based on data from the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) Registry showed that patients with CAKUT progressed to kidney failure at a median age of 31 years⁹⁾. In the study, more than two-thirds of patients with CAKUT notably developed kidney failure in the adult age, and 50% did not require kidney replacement therapy before the fourth decade of life.

Glomerulopathy in children is a result of various disorders including genetic and autoimmune diseases. It causes inflammation and damage to the glomeruli, the filtering units of the kidney, resulting in a rapid decrease in kidney function. According to the CKiD study, patients with glomerulopathy progressed to a composite renal event of kidney failure and/or 50% reduction in GFR after a median follow-up of 3.7 years, which was faster than in patients with non-glomerulopathy (5.2 years)¹⁰⁾. In a retrospective cohort study of children with CKD stages 2–4, patients with glomerular diseases were found to progress more quickly to kidney failure than those with other primary kidney diseases, with the adjusted hazard ratio of 2.9

(95% confidence interval, 1.4–6.1)¹¹⁾.

2. CKD stage

Previous studies reported baseline GFR as the major risk factor for CKD progression in children^{10–12)}. In 2012, the Kidney Disease: Improving Global Outcomes (KDIGO) developed a CKD classification system according to kidney disease causes, GFR category, and albuminuria category. Large-scale observational cohort study, including the CKiD study and the Effect of Strict Blood Pressure Control and ACE inhibition on Chronic Renal Failure Progression in Pediatric Patients (ESCAPE) trial, classified pediatric patients with CKD according to three risk factors: GFR category developed by KDIGO, proteinuria, and glomerular versus non-glomerular diseases¹³⁾. This study showed that median times to a composite kidney event ranged from longer than 10 years for CKD stages 2 to 3a and urine protein/creatinine ratio (UPCR) of <0.5 mg/mg to 0.8 years for CKD stage 4 and UPCR of >2 mg/mg.

3. Perinatal factors

Nephrogenesis commences at 5 weeks of gestation and reaches its peak velocity between 20 and 28 weeks of gestation. Therefore, in preterm infants born with immature kidneys during the period between 20 and 28 weeks, postnatal renal maturation accelerated after birth, with abnormal morphology of nephrons¹⁴⁾. The CKiD study reported that an abnormal birth history, including low birth weight, small for gestational age (SGA), and prematurity, is more common in children with CKD than those in the general population¹⁵⁾. A nationwide cohort study in Sweden revealed that preterm and early-term birth are strong risk factors for the development of CKD from childhood to mid-adulthood¹⁶⁾. In the Norway Birth Registry, low birth weight subjects had an adjusted hazard ratio for kidney failure of 1.61 (95% confidence interval, 1.4–1.98) compared

Table 1. Prospective cohort studies for children with chronic kidney disease

	Country	CKD stage	Age (years)	Number	Follow-up period (years)	Primary outcome	Beginning of year
CKiD	North America	2–4	0.5–17	1,043	15	A decline of eGFR by $\geq 50\%$ or KRT	2003
4C	European countries	3–5	6–17	688	5	Cardiovascular comorbidity	2009
KNOW-PedCKD	Korea	1–5	<20	458	10	A decline of eGFR by $\geq 50\%$ or KRT	2011

CKD, chronic kidney disease; CKiD, Chronic Kidney Disease in Children; eGFR, estimated glomerular filtration rate; KRT, kidney replacement therapy; 4C, Cardiovascular Comorbidity in Children with Chronic Kidney Disease; KNOW-PedCKD, KoreaN cohort study for Outcome in patients With Pediatric Chronic Kidney Disease.

with those without low birth weight¹⁷⁾. This study also showed that subjects with at least two of the three risk factors, including low birth weight, SGA, or preterm birth, have an increased risk for kidney failure. However, evidence that perinatal factors are independent risk factors for the kidney function decline in children with CKD is little. In the CKiD study, low birth weight, SGA, and premature birth were not predictors of more rapid CKD progression¹⁰⁾.

Modifiable risk factors

1. Proteinuria

The presence of proteinuria constitutes a sign of kidney damage, and heavy proteinuria predicts a rapid kidney function decline. Experimental evidence supports the crucial role of proteinuria in accelerating the progression of kidney disease to kidney failure through multiple pathways¹⁸⁾. Urinary proteins themselves can elicit pro-inflammatory and profibrotic effects that directly contribute to chronic tubulointerstitial damage. This tubulointerstitial injury is one of the mediators that lead to CKD progression.

In a cross-sectional analysis of the CKiD study, a decrease in GFR was associated with an increase in UPCR¹⁹⁾. Warady et al. revealed that times to either a 50% decline in GFR or the initiation of kidney replacement therapy were significantly shorter with nephrotic-range proteinuria among children with glomerular and non-glomerular CKD¹⁰⁾. Fuhrman et al. showed that children with proteinuria of ≥ 0.2 mg/mg and albuminuria of ≥ 30 mg/g had a mean eGFR that was 16 mL/min/1.73m² lower than those without proteinuria and albuminuria²⁰⁾. The ESCAPE trial demonstrated that higher levels of proteinuria were associated with a more rapid decline in GFR²¹⁾.

The renin-angiotensin system (RAS) blockade is known to reduce the progressive deterioration of kidney function in patients with CKD through the reduction of blood pressure and proteinuria. Most clinical trials and cohort studies supported the use of RAS blockers in patients with mild to moderate CKD²¹⁻²³⁾. Recently, 4C study showed that GFR declined more rapidly after discontinuation of RAS inhibition compared with that during RAS inhibition (-3.9 vs. -1.5 mL/min/1.73 m² per year)²⁴⁾. However, the renoprotective effect of RAS blockade in non-glomerulopathy remains

controversial. In the ItalKid Project, angiotensin-converting enzyme inhibitor treatment did not significantly modify the naturally progressive course of hypodysplastic nephropathies in children²⁵⁾. Because this study did not have any information concerning proteinuria, it was not sure whether RAS blockade provided an anti-proteinuric effect in children with non-glomerulopathy²⁵⁾. On the other hand, the ESCAPE trial showed that RAS inhibition resulted in reducing urinary protein excretion and lowering blood pressure in both glomerulopathy and non-glomerulopathy²¹⁾.

2. Hypertension

The kidney is a major site for target organ damage of hypertension. Systemic hypertension and glomerular hyperfiltration lead to progressive nephron damage²⁶⁾. Flynn et al. demonstrated that 54% of pediatric patients with CKD were hypertensive, which was defined as either blood pressure of >95 th percentile or as self-reported hypertension plus current treatment with hypertensive medications²⁷⁾. The study group conducted a follow-up analysis 10 years later to compare blood pressure control over two time periods among participants enrolled in 2005–2008 and 2010–2013²⁸⁾. In this study, no significant differences were found in hypertension between the two time periods, suggesting that hypertension remains undertreated and under-recognized in children with CKD. Warady et al. revealed that elevated blood pressure was associated with a significant reduction in time to kidney events in patients with both glomerular (67% reduction) and non-glomerular disease (38% reduction)¹⁰⁾. This finding emphasized the importance of aggressive BP control, particularly in patients with glomerular causes of CKD.

The ESCAPE trial showed that intensified blood pressure control conferred a substantial benefit regarding kidney function among children with CKD stages 2–4²¹⁾. The trial was designed to compare intensified blood pressure control (target <50 th percentile) with conventional control (50th–90th percentile) using an angiotensin-converting enzyme inhibitor. Based on the results of this trial, the KDIGO guideline recommends that the blood pressure treatment target for children with CKD is systolic and diastolic blood pressure of less than the 50th percentile for gender, age, and height²⁹⁾.

3. Dyslipidemia

The prevalence of dyslipidemia in children with CKD is high, being present in 39%–65% of patients³⁰. The KNOW-PedCKD study reported that 61.5% of pediatric patients with CKD stages 1–5 had dyslipidemia, and CKD stage $\geq 3b$ had a significantly increased risk for high triglyceride level³¹. In the CKiD study including children with CKD stages 2–4, 45% of patients with CKD had dyslipidemia, and lower GFR was associated with dyslipidemia³².

While dyslipidemia is a well-known cardiovascular disease risk factor commonly found in children as well as in adults, the relationship between dyslipidemia and CKD progression in children is uncertain. Warady et al. reported that dyslipidemia was significantly related to CKD progression in children with non-glomerulopathy, but not in those with glomerulopathy¹⁰. Longitudinal analysis in the CKiD study showed that decreases in GFR during follow-up were significantly associated with concomitant decreases of HDL cholesterol in children with non-glomerular CKD and increases of non-HDL cholesterol in children with glomerular CKD³³. In this study, dyslipidemia was also associated with concomitant increases in proteinuria and body mass index. Future studies are needed to clarify the relationship between CKD progression and dyslipidemia in children with CKD.

Dyslipidemia is managed through therapeutic lifestyle changes and pharmacologic treatment. Although the evidence is weak on lifestyle modifications are effective to improve dyslipidemia in children with CKD, these are unlikely to cause harm and can promote better health³⁴. Statins and ezetimibe are approved by the USA and Korean Food and Drug Administration to treat dyslipidemia in the pediatric population. However, the 2013 KDIGO guideline does not recommend the lipid-lowering agent as the first-line treatment in children under 18 years with CKD due to the lack of evidence³⁵.

4. Hyperuricemia

Hyperuricemia is associated with the development and progression of CKD. Experimental studies supported that hyperuricemia plays a role in CKD progression through direct kidney injury, including oxidative stress, endothelial cell dysfunction, and epithelial-to-mesenchymal transition of tubular cell³⁶. Rodenbach et al. reported that hyperuricemia is an independent risk factor for the faster progres-

sion of CKD in children. In this study, pediatric patients with CKD with uric acid levels of 5.5 to 7.5 or >7.5 mg/dL had 17% or 38% shorter times to CKD progression, respectively, compared with those with uric acid levels of <5.5 mg/dL³⁷. The Taiwan Pediatric Renal Collaborative Study showed that hyperuricemia significantly increased the risk of CKD progression in children with CKD because of a structural abnormality or genetic disease¹².

Treating asymptomatic hyperuricemia to slow down the progression of CKD is controversial, given the conflicting results in several clinical studies³⁶. A meta-analysis study concluded that data suggesting uric acid-lowering therapy may prevent CKD progression is limited, and larger clinical trials are needed to evaluate the benefits and risks of uric acid-lowering therapy in CKD³⁸. In a prospective cohort study in adults, hyperuricemia appears to be an independent risk factor for CKD progression, but urate-lowering agents did not show a renoprotective effect³⁹.

5. Anemia

Anemia is a common complication of CKD and is associated with several clinical consequences, including mortality, cardiovascular morbidity, and growth failure^{40,41}. Two prospective cohort studies for children with CKD showed that 40%–45% of patients had anemia and the hemoglobin level decreases as GFR declines^{42,43}. Anemia and resulting tissue hypoxia could increase endothelial injury and stimulate the release of profibrotic cytokines. GFR declined more rapidly in adolescent patients with CKD with significant anemia. In the CKiD study, anemia was associated with an accelerated decline of $7.8 \text{ mL/min/1.73m}^2$ in adolescents with CKD aged 11–18 years compared with the decline rate in those without anemia⁴⁴. Warady et al. reported that time to the composite renal event was significantly shorter with anemia by 45% among children with non-glomerular CKD¹⁰.

In the KNOW-Ped CKD study, only 21.6% and 36.6% of children with anemia were treated with erythropoietin-stimulating agent (ESA) and iron supplementation treatment, respectively⁴³. This finding suggests the importance of identifying anemia and iron deficiency and actively correcting these in pediatric patients with CKD. In a randomized controlled study in adults with predialysis CKD, early treatment of ESA targeting at a higher hemoglobin

level significantly slowed the progression of CKD and delayed the initiation of kidney replacement therapy⁴⁵⁾. However, high serum erythropoietin level is associated with the risk of cardiovascular events in adults⁴⁶⁾. Although the question of appropriate target hemoglobin levels in children remains under debate, the KDIGO guideline recommends that Hb targets with ESA treatment should be kept within the range of 11.0–12.0 g/dL⁴⁷⁾.

Conclusions

To date, several risk factors for the progression of pediatric CKD are known. Modifiable risk factors for CKD progression in children should be identified early and treated adequately. Recognition of non-modifiable risk factors is also important since patients at high risk could particularly benefit from strict control of remediable risk factors including hypertension and proteinuria. Developing a prediction model for the progression of CKD is needed to support clinical decision making. Additionally, further research is necessary to determine the effects of risk factor interventions on the progression of CKD in children.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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