Original Article

Are My Pediatric Patients at Increased Risk of Developing Chronic Kidney Disease?

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Abstract

Chronic kidney disease (CKD) is an underrecognized and often undiagnosed cause of morbidity and mortality. Many children and adolescents are at increased risk of developing CKD as they mature and age, secondary to conditions commonly cared for by pediatric health professionals. Prematurity, diabetes mellitus, hypertension, congenital heart disease, sickle cell disease and trait, severe obesity, cancer chemotherapy, other drug toxicities, and systemic situations that may cause acute kidney injury such as sepsis or extracorporeal membrane oxygenation therapy predispose to potential CKD. Clinicians should be aware of these conditions in order to screen for CKD, choose non-nephrotoxic treatments for these children whenever possible, and treat or refer those who have early signs of CKD.

Keywords

kidney disease, prematurity, proteinuria, diabetes mellitus, hypertension, obesity, sickle cell disease

Pediatricians rarely encounter chronic kidney disease (CKD) and, in general, may think of CKD as a problem for internists and nephrologists. However, many children and adolescents are at increased risk of developing adult CKD, secondary to conditions commonly cared for by pediatric health professionals. Kidney-related conditions such as congenital abnormalities of the kidney or ureter (CAKUT), a history of resolved glomerulonephritis or hemolytic uremic syndrome or repeated upper urinary tract infections are well-recognized CKD risk factors,[1,2] even if kidney function appears to be normal in adolescence.[3] This report examines nonprimary kidney diagnoses commonly managed by pediatric professionals, which may increase the risk of subsequent CKD, including those systemic events that may lead to acute kidney injury (AKI). The increased awareness of the potential for kidney damage will allow pediatric practitioners to appropriately screen, counsel, and treat those patients at risk.

Chronic kidney disease is common, often underdiagnosed, and expensive. In the United States, CKD is the ninth most common cause of death[4] and, in 2017, cost Medicare more than $120 billion.[4] From 2009 to 2010, CKD cost the British National Health Service (NHS) an estimated £1.45 billion representing about 1.3% of NHS spending, and an estimated 19 000 CKD-related cardiovascular (CV) complications cost about £175 million.[5] Hypertension and diabetes, both of which can begin in childhood, are the most common causes of adult CKD.[6] The United States Renal Data System (USRDS) estimates that about 15% of the adult population in the United States has some degree of CKD, but only 10% of those are aware of their disease and/or its implications.[6] The NHS estimates that 6% to 8% of the English population have CKD stages 3 to 5.[5] In an effort to address this problem in the United States, a Presidential Executive Order issued July 2019 states in part: "It is the policy of the United States to: (a) prevent kidney failure whenever possible through better diagnosis, treatment, and incentives for preventive care."[7] Similarly, a multicountry European position paper stresses the importance of prevention and early detection of CKD.[8] Pediatricians and family practitioners have important roles to meet this objective, as they are likely to have patients in their

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practice at risk of CKD from the clinical situations described in this report.

Barker and colleagues stimulated intense interest in the pediatric origins of adult disease with their seminal demonstrations in the 1980s of the inverse relationships between low birth weight, coronary heart disease, hypertension, and type 2 diabetes.[9] Similarly, we now know that nephron endowment, or the number of functional nephrons an individual possesses at birth, affects later risk of CKD.[10-14] Nephron development is negatively affected by genetic, epigenetic, and environmental factors, including gestational age, maternal nutrition, and ureteroplacental insufficiency.[1,10,11,15] As humans cannot regenerate nephrons, a limited number at birth or destruction by disease provides the basis for development of CKD. Nephrons compensate by hypertrophy and hyperfiltration, often marked by development of microalbuminuria (MA) and later proteinuria, leading to renal tubular damage and glomerulosclerosis with eventual functional loss.[16-19] A urine dipstick of ≥1+ diagnoses proteinuria, if confirmed by a carefully collected first morning urine protein/creatinine (mg/mg) >0.2.[20,21] MA is defined as a first morning urine >30 mg albumin/mg creatinine.[20] The antihypertensive drugs, angiotensin converting enzyme inhibitors (ACEIs), and angiotensin receptor blockers (ARBs) are hypothesized to limit intraglomerular hyperfiltration by altering hemodynamics and are well recognized to decrease proteinuria and retard the development of CKD in adults and children.[17,22,23]

Children and adolescents born prematurely constitute the most commonly encountered patients at risk for CKD and its consequences cared for by pediatric clinicians. Human nephronogenesis continues until 34 to 36 weeks gestation with about 60% of nephrons developing during the third trimester. Consequently, the earlier in gestation a premature infant is born, the more likely they are to have fewer functional nephrons, and consequently are at increased risk of developing CKD later in life.[10,11,13,15,24] A national cohort study of 4.2 million live births in Sweden shows a 3-fold increased incidence of CKD in adults aged 20 to 43 years born <28 weeks gestation, and a 2-fold increase in those born 28 to 36 weeks gestation compared with full-term infants.[14] Using low birth weight as a surrogate for lower nephron number, multiple studies have shown associations between low nephron number and higher risk of proteinuria, hypertension, cardiovascular disease (CVD), and CKD.[13,14,25,26] A nationwide survey in Japan of infants born <2500 g showed a relative risk of CKD in children <15 years of age of 4.73 (95% confidence interval = 3.91-5.73) after correction for children with CAKUT.[27] As discussed in detail below, the risk of later CKD in premature and low-birth-weight infants is compounded by the high incidence of AKI during neonatal intensive care unit (NICU) care.

Search Strategy

References for this review were identified through searches of PubMed and the authors' personal files with the search terms of the 7 clinical scenarios that the authors agree are the most common non-primary kidney or urological conditions that may lead to CKD. These clinical situations are prematurity, diabetes mellitus, hypertension, AKI, severe obesity, sickle cell disease (SCD), congenital heart disease (CHD), sepsis, and s/p exposure to nephrotoxins as in s/p cancer chemotherapy. They were identified by discussions with colleagues and personal experiences and are all well supported by cited references, with emphasis on most recent or "classical" articles. Only articles published in English or with English language abstracts were reviewed.

Results

Acute kidney injury occurs if renal oxygenation is compromised by decreased perfusion, interruptions in metabolic pathways, or systemic disease and may lead to CKD.[28-31] AKI is a frequent problem in hospitalized children and increases the mortality rate in children who develop AKI in the critical care setting.[32] The AWARE study reported that 26.9% of 4683 critically ill children developed AKI by 28 days after admission using Kidney Diseases Improving Global Outcomes (KDIGO) criteria for AKI.[33] Repeated episodes of AKI, as frequently occurs in an ICU or NICU setting, markedly increase the risk of irreversible renal damage from nephron loss leading to CKD.[34,35] Multiple disordered repair mechanisms lead to fibrosis of the renal interstitium and eventual nephron loss.[34,35] Mammen et al found that 1 to 3 years following AKI in 126 children without preexisting kidney disease, despite all having return of serum creatinine to normal, 9.5% had MA or proteinuria, 38% had decreased estimated glomerular filtration rate (eGFR), and 3.2% had hypertension.[36] Similarly, 18-year-old Israeli army recruits with a remote history of AKI, such as postinfectious glomerulonephritis, have an increased incidence of hypertension and proteinuria indicating CKD.[3] About 10% of children between 6 months and 18 years of age admitted for treatment of severe sepsis had AKI and 6% were left with CKD.[37] Thus, AKI can lead to CKD in many different settings in neonates and children.

Premature and very-low-birth-weight infants are especially at risk for AKI while undergoing NICU care, including hypoxia, sepsis, and exposure to nephrotoxic medications. The multicenter observational AWAKEN

study of 2022 NICU babies showed that AKI was diagnosed in 48% born at 22 to 28 weeks and 18% born at 29 to 35 weeks gestation.[38] An autopsy study of 56 premature infants found fewer nephrons in premature as compared with term infants due to interruption of glomerulogenesis, with this difference more striking in those infants with a history of AKI.[39] Recent studies have confirmed that infants who survive episodes of AKI and recover kidney function are at risk for long-term sequelae including CKD, hypertension, and CVD.[13,36,38,40,41] As a result, more emphasis has been placed on early recognition and prevention of AKI in this vulnerable population.[10,11,13,42,43]

Hypertension is the leading cause of CKD in adults.[6] Pediatric guidelines are well established for screening, diagnosis, and evaluation of the estimated 4% of children worldwide who are hypertensive.[44-47] Longitudinal data support a strong tendency for hypertension to track from the pediatric age group into adulthood.[48] Hypertension in teenagers has been shown to increase the risk of end-stage renal disease (ESRD) in middle-aged adults in large studies in Sweden and Israel.[3,45]

Persistent hypertension has been associated with CV target organ damage in both adults and children.[49] CVD causes significant morbidity and mortality in patients with CKD.[6] Given the adverse effects of hypertension and those of CKD on CV health including ventricular hypertrophy, vascular calcification, and arterial stiffness, it is imperative to identify and intervene. Effective treatment to decrease proteinuria from hypertension-related hyperfiltration limits CVD risk[50,51] and retards the rate of decline of renal function in pediatric patients with CKD.[52] The association of hypertension, renal injury, and albuminuria has been somewhat inconsistent in several small pediatric studies, and so, monitoring MA cannot currently be recommended for serial assessment of patients with hypertension as it is in the adult population.[53]

Diabetes is the second most common cause of CKD in the United States after hypertension.[6] Between 2003 and 2012, the incidence of type 1 diabetes mellitus (T1DM) increased from 19.5 in 2003 to 21.7 cases/100 000 youth/year and type 2 diabetes mellitus (T2DM) from 9.0 in 2003 to 12.5 cases/100 000 youth/year.[54] The Centers for Disease Control and Prevention estimates that about 5000 new pediatric cases of T2DM develop annually in the United States.[4] In diabetes, MA and hypertension are independent but additive risks of CKD. The multicenter Treatment Options for T2DM in Adolescents and Youth (TODAY) study reported that 33.8% had hypertension and 16.6% had MA at 3.9 years of follow-up.[55] Another study of youth with T1DM found that 16.1% had albuminuria and 12.3% had hypertension.[56] The American Diabetes Association guidelines recommend annual screening for MA in children with T1DM after 5 years of disease or age 10, whichever comes first, and recommends screening for MA at diagnosis of T2DM and annually thereafter.[57] Treatment of hypertension and/or MA with an ACEI or an ARB is recommended to decrease risks of progression of CKD and CVD.[57] Bariatric surgical treatment of obesity in severely obese T2DM adolescents compared with medical therapy decreases the likelihood of CKD.[58] In adult diabetic patients, the antiglycemic sodium-glucose co-transporter-2 (SGLT-2) inhibitors lower blood pressure and retard progression of CKD.[59,60] Clinical trials of SGLT-2 inhibitors in adolescents with T2DM are underway.

Obesity is the third most common predictor leading to ESRD in adults with odds ratios of 7.72 for proteinuria, 3.97 for hypertension, and 3.53 for obesity.[3,61] The National Health and Nutrition Examination Survey (NHANES) reports that in the United States, 13.9% of 2 to 5 year olds, 18.4% of 6 to 11 year olds, and 20.6% of 12 to 19 year olds are identified as obese.[62] Childhood obesity tracks into adulthood with obese children and adolescents being 5 times as likely to be obese adults.[63] Obesity often causes hypertension and/or T2DM, well-recognized antecedents of CKD discussed elsewhere in this report.

Obesity is hypothesized to cause hyperfiltration resulting in focal segmental glomerulosclerosis,[64] as well as renal metabolic disturbances due to the effects of altered adipokine levels associated with obesity.[65] Patients with preexisting decreased nephron mass who become obese have an even greater risk of progressive CKD.[10,11,13,66] Weight loss interventions, including bariatric surgery,[58,67] have been shown to reduce albuminuria, the most common early manifestation of CKD in obesity-related nephropathies, and lessen the risk of ESRD in both adolescents and adults.[68] As in other conditions, the hemodynamic modulating ACEIs and ARBs are renoprotective in obese proteinuric patients.[69]

Children with congential heart disease (CHD) are at increased risk for CKD to develop in childhood or later as adults.[70,71] Risk increases based on the severity of the CHD with higher risks in those requiring surgery, having cyanotic heart disease,[71-74] requiring extracorporeal membrane oxygenation treatment,[75] or acute renal replacement therapy.[76] In studies of adult patients with CHD, as many as 50% had CKD measured by decreased eGFR.[77] AKI is common following cardiac surgery and can occur in as many as 50% of children postoperatively.[78] Following cardiac surgery, 17% of CHD children experience hypertension, 8% proteinuria, and/or 13% decreased eGFR.[71] The 5-year cumulative incidence of CKD for pediatric patients with cardiac surgery–associated AKI was 12% compared with 3% of cardiac surgery children without AKI.[71]

Studies in CHD patients suggest that findings of renal injury may be identified early in childhood by close monitoring for hypertension, proteinuria, and, possibly in the near future, biomarkers.[79] Serum creatinine may underestimate renal decline depending on height, nutritional status, and body mass index of the patient, as these parameters are occasionally diminished in patients with CHD.[80]

Sickle cell disease is universally associated with progressive concentrating defects, and hematuria is common.[81,82] ESRD occurs in 4% to 7% of patients, most commonly in the third decade of life.[82] Deterioration of renal function is nearly always associated with albuminuria. Multiple studies have demonstrated a prevalence of albuminuria of 18% or more occurring as early as the first decade of life.[83-86] Elevated blood pressure and CKD were identified in 16.7% and 8.3%, respectively, in a cross-sectional study of children with SCD.[87] As in other proteinuric renal diseases, ACEIs and ARBs reduce MA and proteinuria in adults and children with SCD and retard loss of renal function.[88-90] Hydroxyurea, which limits the frequency of vaso-occlusive complications of SCD by reducing intravascular sickling of red blood cells, reduces, at least in the short term, MA in both SCD children and adults.[91]

Sickle cell trait is well recognized as a risk factor for hematuria, renal papillary necrosis, concentration defects, and renal medullary carcinoma.[92] A recent report suggests a 2-fold lifetime increase in the risk of ESRD over a comparable population without sickle cell trait.[93]

Many therapeutic medications and environmental exposures are potentially nephrotoxic, especially with high doses and/or long-term use.[94,95] Cancer therapeutic agents may produce dose and/or duration-related kidney damage with a higher risk for CKD associated with high-dose cisplatin, carboplatin, and/or ifosfamide therapy.[96,97] Kidneys may inadvertently be exposed during radiation therapy for abdominal or retroperitoneal malignancy causing interstitial fibrosis and loss of renal function. Pediatric cancer survivors have high rates of subclinical renal dysfunction, and as many as 30% to 50% will develop CKD in their lifetime.[97] In cancer survivors, MA is significantly more prevalent on urine screening than either hematuria or proteinuria.[98]

Aminoglycoside antibiotics and antifungals such as amphotericin can cause AKI.[99] Toxic levels of the heavy metals lead, cadmium, uranium, and mercury damage the renal tubules, with resulting nephron loss.[100] Some data suggest that chronic environmental exposure to low levels of heavy metals, especially cadmium, may predispose to CKD.[101,102] Nonsteroidal anti-inflammatory drugs can decrease renal blood flow resulting in AKI, especially in patients with preexisting renal damage or renovascular disease.[103,104] Lithium at therapeutic levels causes polyuria due to loss of urine concentrating ability, and toxic levels may permanently damage the collecting ducts leading to nephrogenic diabetes insipidus and potential nephron loss.[105]

Discussion

Exposure to childhood events that increase the risk of CKD are potentially additive.[10,11,13] Thus, the former premature infant delivered at 26 weeks because of maternal eclampsia, who received several courses of aminoglycosides, and who as an adolescent becomes obese and develops T2DM is at high risk of developing CKD. Although many of these at-risk patients may not develop signs or symptoms of CKD until adulthood, it is incumbent on child health professionals to mitigate, whenever possible, the potential for adult morbidity.[3,10] Optimizing blood glucose levels in diabetes, controlling obesity, avoiding dangerous levels of nephrotoxic drugs, and controlling hypertension are obvious goals that may limit kidney damage.[10]

Microalbuminuria and proteinuria are early signs of CKD and are readily measured in a carefully collected first morning urine.[20,21] Mitigating hyperfiltration with ACEIs or ARBs decreases the proteinuria and retards the progression of CKD.[10,23] Since early diagnosis and appropriate therapy lessens the risks of progression of CKD, child health professionals should consider urinalyses during routine health maintenance visits for those patients at risk and treat or refer to nephrology if a positive result is confirmed. Biomarkers for early diagnosis of AKI and novel therapies such as SGLT-2 inhibitors in diabetes and hydroxyurea in SCD hold promise for earlier diagnosis and more effective therapies to prevent or limit CKD in the near future.[59,60,91]

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Author Contributions

WP conceptualized and designed the study. WP, SK, FB, SJ drafted and critically revised the manuscript for important intellectual content. All authors give final approval to the manuscript, and have agreed to be accountable for all aspects of the work.

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