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REVIEW

Childhood risk factors for adulthood chronic kidney disease

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Abstract

Chronic kidney disease (CKD) is a major public health challenge, affecting as much as 8 to 18% of the world population. Identifying childhood risk factors for future CKD may help clinicians make early diagnoses and initiation of preventive interventions for CKD and its attendant comorbidities as well as monitoring for complications. The purpose of this review is to describe childhood risk factors that may predict development of overt kidney disease later in life. Currently, there are multiple childhood risk factors associated with future onset and progression of CKD. These risk factors can be grouped into five categories: genetic factors (e.g., monogenic or risk alleles), perinatal factors (e.g., low birth weight and prematurity), childhood kidney diseases (e.g., congenital anomalies, glomerular diseases, and renal cystic ciliopathies), childhood onset of chronic conditions (e.g., cancer, diabetes, hypertension, dyslipidemia, and obesity), and different lifestyle factors (e.g., physical activity, diet, and factors related to socioeconomic status). The available published information suggests that the lifelong risk for CKD can be attributed to multiple factors that appear already during childhood. However, results are conflicting on the effects of childhood physical activity, diet, and dyslipidemia on future renal function. On the other hand, there is consistent evidence to support follow-up of high-risk groups.

Keywords Chronic kidney disease · End stage kidney disease

Introduction

Chronic kidney disease and progressive loss of kidney function constitute a major public health challenge, with a worldwide prevalence of 8 to 18% [1, 2]. The rising prevalence of CKD is of great concern as patients with CKD are at increased risk for all-cause mortality, end-stage renal disease (ESRD) [3], and cardiovascular disease, even with a small reduction in kidney function [4]. Kidney failure tends to develop slowly and without symptoms in most cases. Patients usually become aware of having CKD too late in its course to intervene. Consequently, identifying risk factors for CKD may help clinicians make early diagnoses, initiate preventive interventions for CKD and its attendant comorbidities and facilitate monitoring for complications.

Universal population screening for CKD is not globally recommended for children according to the most recent AAP (American academy of pediatrics) guidelines (https://www.aap.org/en-us/Documents/periodicity_schedule.pdf), although screening programs for children in other countries around the world are routinely performed [5].

In addition to well-established adulthood CKD risk factors such as diabetes and hypertension, there are a multitude of childhood risk factors associated with the future onset and progression of CKD. The purpose of this review is to describe those childhood risk factors that may predict the development of overt kidney disease later in life. Consequently, biomarkers and risk factors in children with established CKD are not discussed.

Epidemiology of CKD in children and adults

The primary causes of early-onset CKD in children differ substantially from adult-onset CKD. To date, the most

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common pediatric CKD etiologies include (1) congenital anomalies of the kidneys and urinary tract (CAKUT) (~ 50%), (2) glomerular diseases (~ 20%), (3) renal cystic ciliopathies (~ 5%), (4) hemolytic uremic syndrome (~ 2%), and (5) ischemic renal failure (~ 2%), together encompassing over 75% of the entire pediatric CKD population (Table 1) [6, 7]. Adult-onset CKD is attributed mainly to diabetes and hypertension followed by glomerular diseases and exposure to nephrotoxins (Table 1) [2, 8].

Given the high prevalence of diabetes and hypertension in adults and the fact that most adults with CKD do not undergo kidney biopsy, it is plausible that many CKD etiologies in adults can additionally be attributed to other risk factors, including early life-related risk factors. Moreover, these risk factors can also be the culprit for adult onset CKD in many individuals in whom the etiology is undetermined.

In the adult population, fewer than 2% of people with CKD progress to ESRD as persons with CKD are five to ten times more likely to die, mainly from cardiovascular disease, before reaching ESRD [2]. This worrisome fact further emphasizes the clinical need to identify at risk patients early on (Table 2).

Genetic factors

Understanding of the genetic underpinnings of CKD has grown significantly in the past 15 years. Historically, the genetic risk for CKD has long been appreciated by familial clustering, as well as population disparities of CKD and ESRD across many common CKD etiologies [9, 10]. In general, the genetic risk of CKD can be classified according to its penetrance. At one extreme, there are rare monogenic diseases with Mendelian inheritance with high penetrance disease causative alleles. Such Mendelian monogenic disorders are the most common underlying cause for CKD and ESRD in children [11]. As such, these genetic abnormalities confer clear risk for childhood as well as adulthood onset CKD. To date, a large fraction of early-onset CKD is considered to be monogenic in origin. So far, ~ 450 single-gene disorders (monogenic) are known to cause CKD, explaining ~ 30% of cases in pediatric cohorts and ~ 5–30% in adult cohorts [7, 12]. In addition, some of the childhood genetic contribution for future CKD might be partly attributable to low penetrance genetic risk alleles acting in concert with environmental triggering factors that eventually lead to adult onset CKD [13]. Such risk alleles include for instance the *APOL1* locus [14, 15] the *PLA2R* [16] locus, or the *UMOD* locus [17]. The risk of all-cause CKD has also been studied in several genome wide association studies (GWAS) aiming to asses genetic risk score for all-cause CKD [18].

Uncovering the underlying genetic causes of CKD during early childhood by more widespread use of genetic testing programs will improve diagnostic accuracy and contribute to "precision medicine" approaches. Importantly, genetic testing might reduce the time to diagnosis and establish the cause of CKD long before the development of severe symptoms. Nevertheless, clinicians must be able to correctly interpret genetic findings in order to make the best decisions regarding patient care. In this respect, remaining challenges include the attribution of causality for rare variants, as well as the identification and reporting policy of incidental findings. Moreover, the cost effectiveness of population genetic screening programs should be quantified before it can be established as standard clinical practice [19].

Perinatal factors

In the late 1980s, Barker et al. introduced the concept of intrauterine malnutrition, marked by low birth weight (LBW), and future risk for type 2 diabetes, hypertension, dyslipidemia, and cardiovascular disease in adult life [20, 21]. This concept was further extended by Hoy and Nelson as well as others [22, 23] to include kidney-related implications.

Prematurity and low birth weight

To date, numerous epidemiological studies, mostly birth cohorts, have shown a strong association between low birth weight (< 2500 g) and prematurity and the development of CKD in adulthood [24–27]. A meta-analysis of 31 cohorts and

Table 1 Leading categories of etiologies of CKD

Adults*	Pediatric
Diabetes**	Congenital anomalies of the kidneys and urinary tract (CAKUT)
Glomerulonephritis	Glomerular disease
Hypertension	Renal cystic ciliopathies
Autosomal dominant polycystic kidney disease	Hemolytic uremic syndrome
Other cystic and tubulointerstitial nephropathy	Ischemic renal failure

*Relative contribution of each category varies with geographic region and race

**Diabetes accounts for 30-50% of all cases of adult CKD worldwide [2]

Table 2 Risk factors for chronic kidney disease in childhood and adulthood

Category
Genetic factors
Ethnicity
Family history of kidney diseases
Monogenic kidney diseases
Risk alleles
Perinatal factors
Prenatal exposure to nephrotoxins
SGA
Prematurity
Major childhood kidney disease and their impact in adulthood
CAKUT
Glomerulopathies
Cystic kidney diseases
Tubulointerstitial disorders and other childhood kidney conditions
Acute Kidney Injury of any cause
Childhood onset of chronic conditions conferring future risk for CKD
Diabetes
Hypertension
Hyperlipidemia
Obesity
Cancer
Lifestyle factors
Diet
Lack of physical activity
Smoking
Socioeconomic status

case-control studies has shown that individuals with LBW have an overall greater risk of developing CKD in later life (overall odds ratio (OR) of 1.73, 95% confidence interval (CI), 1.44 to 2.08) [28]. Subsequent observations showed similar results [29]. Of note, this association has only been described in retrospective population-based or case-control studies, and the terms LBW and prematurity were used interchangeably. The central hypothesis for this association is related to low nephron mass (endowment) secondary to incomplete nephrogenesis [22] which typically occurs between the 5th and 36th weeks of gestation.

Furthermore, one should take into consideration additional risk factors relevant to premature infants in the context of acute kidney injury (AKI) and CKD continuum [30]. Premature neonates have an inherent susceptibility to kidney injury given low GFR, impaired renal auto regulation, and tubular immaturity [31]. Common AKI etiologies during this period include exposure to nephrotoxins such as gentamicin and nonsteroidal anti-inflammatory drugs [31], nephrocalcinosis secondary to increased urinary calcium excretion of furosemide therapy [32], and prolonged use of parenteral nutrition and oxygen [33] as well as renovascular disease due to umbilical catheterization complications [34].

Major childhood kidney diseases and their impact in adults

CAKUT, glomerular diseases, and renal cystic conditions account for most of kidney diseases during childhood. While CKD during childhood is clearly related to CKD during adulthood, mild forms of childhood kidney diseases can go unnoticed. In fact, the long-term risk for developing CKD in adulthood after childhood kidney disease that had not progressed to CKD in childhood was mostly unknown until recently. Our group showed that a history of clinically evident kidney disease in childhood, even if renal function was apparently normal in adolescence, was associated with a significantly increased risk of ESRD. This observation suggests that kidney injury or structural abnormality in childhood has long-term consequences [35]. Importantly, this future CKD risk may be attributed not only to the original primary childhood kidney disease etiology, but also by affecting the renal functional reserve, to one's lifelong risk for CKD of any cause.

CAKUT

The prevalence of CAKUT, which is the leading cause of kidney disease in children, is 0.4–4.0 per 1000 newborns [35, 36]. The understanding of the genetic basis of CAKUT has grown significantly in the past 15 years. To date, more than 40 different monogenic causes for human CAKUT have been described [37, 38]. Additionally, copy number variations were identified among 10–16% of individuals with CAKUT, most commonly involving the *HNF1B* or the DiGeorge/velocardiofacial locus [39]. Many of these CAKUT genes encode transcription factors and follow a dominant pattern of inheritance with incomplete penetrance and variable expressivity [37]. Genetic alternations in hepatocyte nuclear factor 1-beta (*HNF-1β*) which is involved in the development of kidneys, liver, pancreas, and urogenital tract, are the most frequent monogenetic cause of CAKUT found in 10–30% of patients [40]. Other established genes that if mutated would cause CAKUT include *PAX2*, *EYA1*, *SALL1*, *GATA3*, and *MUC1* [37, 38]. The full spectrum of single-gene causes of CAKUT are beyond the scope of this review and have been recently reviewed [37, 38, 41]. Regardless of the underlying genetic etiology, our observations [42] as well as others [43] strongly suggest that CAKUT with normal kidney function during childhood may confer future risk for CKD. This has been shown for children with single kidney [44] Posterior urethral valves and renal hypoplasia.

Glomerulopathies

Glomerular diseases during childhood may be a result of various disorders. Some of the children have clear residual or relapsing kidney disease manifested by decreased glomerular filtration rate, urine findings, or hypertension. However, most children with a first event of glomerular pathology have a favorable prognosis with complete resolution of all signs and symptoms. Still, among healthy adults, the long-term sequelae of past resolved childhood glomerular injury are incompletely understood. Among healthy individuals, the two most common resolved childhood glomerular diseases are acute glomerulonephritis and steroid-sensitive nephrotic syndrome. Previous case series have shown good long-term prognosis for children with these conditions. Still, 3.5% to 21.1% of patients with glomerulonephritis [45, 46] and 2.6% with nephrotic syndrome [47] have been reported to develop either persistent urinary abnormalities or hypertension [48]. In a recent population-based historical cohort study [35], we found that the incidence rate of ESRD among participants who had a history of glomerular disease in childhood was 16.3 cases per 100,000 person-years, about four times higher than the incidence rate among participants with no such history.

Childhood onset of steroid resistant nephrotic syndrome, as opposed to steroid sensitive nephrotic syndrome, has much greater subsequent risk for adulthood CKD. Mutations in genes encoding podocyte-associated proteins have been implicated in about 30% of steroid resistant nephrotic syndrome (SRNS) in children. More than 50 monogenic causes have been identified and recently reviewed in multiple papers [49]. The most common single gene etiologies for SRNS in children are *NPHS1*, *NPHS2*, *WT1 PLCE1*, and *LAMB2* [49]. The most common single gene etiologies for adulthood onset SRNS include *INF2* and *TRPC6* [49].

Another example of childhood glomerular disease with adulthood sequela is Alport syndrome. The risk for CKD, in persons with Alport's syndrome, is highly dependent on the *COL4A* mutation type as well as on early introduction of treatment (i.e., ACE inhibitors) [50]. Interestingly, it has recently been shown in multiple studies that undiagnosed mutations in *COL4A* are responsible for adulthood onset CKD [51–53].

Renal cystic diseases

Renal cystic diseases are a group of inherited diseases which lead to CKD both during childhood and adulthood. These diseases are genetically very heterogeneous and can be caused by mutation in one of ~ 90 different genes [54]. In adults, the most common genetic forms include autosomal dominant polycystic kidney disease (ADPKD) which can be secondary to mutations in *PKD1*, *PKD2*, *GANAB* [55], or *DNAJB11* [56]. These persons during childhood can have normal renal phenotype or only single renal cysts [57]. In children and young adults, renal cystic diseases (also known as nephronophthisis-related ciliopathies) are mostly caused by deletions or mutations in the *NPHP1*—known to account for 20–25% of all cases [58]. The full genetic spectrum of renal cystic diseases are discussed in more details by Braun et.al [54].

In summary, recent studies support the notion that mild or resolved childhood kidney diseases confer a future risk of ESRD [42]. These findings are consistent with multiple recent observations of increased CKD among adults [30] [59] as well as children [60, 61], who previously had AKI, regardless of its underlying etiology. Importantly, many of these childhood kidney diseases are genetic in origin; therefore, early genetic analysis can lead to early identification of high-risk pediatric populations which will allow for early clinical monitoring.

Childhood onset of chronic conditions conferring future risk for CKD

Limited information about the natural course of CKD progression in children with chronic conditions is available. Of the traditional adult-onset CKD risk factors (such as obesity, diabetes, and hypertension), some may actually have had deleterious effect during childhood. Childhood onset of these chronic conditions adds additional exposure years, and as a result poses significant risk for adulthood CKD.

Body mass index

In recent decades, overweight and obesity have reached pandemic proportions. The 2015 updated analysis of the Global Burden of Disease Study reported a total of 107.7 million obese children [62]. In a systemic review and meta-analysis that was published in 2017 and included 39 cohort studies, the authors reported that obesity increased the relative risk of developing low glomerular filtration rate (GFR) and albuminuria, in more than 600,000 participants enrolled in the analysis, over a mean follow-up period of 6.8 years [63]. In a population-based historical cohort study with over 1 million adolescents without a past or present diagnosis related to kidney disease, increased body mass index (BMI) at age 17 was strongly associated with the increased incidence of future ESRD. Overweight was associated with an hazard ratio (HR) of 3.00 (95% CI, 2.50–3.60) and obesity with an HR of 6.89 (95% CI, 5.52–8.59) for all-cause treated ESRD [64].

Hypertension

Similarly, it has been shown that elevated blood pressure in childhood is associated with subsequent adult hypertension [65]. Childhood hypertension and prehypertension have been suggested to confer future risk for adulthood CKD in a large population based study of over 2 million adolescents ages 16–19 years [66].

Hyperlipidemia

Another possible risk factor for progressive of CKD is dyslipidemia. Epidemiological studies support dyslipidemia as an independent risk factor for the progression of CKD. The dyslipidemic pattern differs between the major renal disease entities, and the degree of dyslipidemia parallels the degree of renal function impairment. However, the evidence for dyslipidemia as an independent risk factor for renal disease development or progression in adults, although it is not well established by some studies [67] and only few reports support this association [68].

Childhood onset diabetes

Children with type 1 diabetes (T1D) are at increased risk for diabetic nephropathy, potentially leading to ESRD. For these patients, ESRD remains the major cause of premature morbidity and mortality as lifetime risk of ESRD is estimated at 10–15%. Typically, progressive renal disease and ESRD develops decades after the onset of T1D. The younger age of T1D patients at onset of ESRD, compared to adult patients with type 2 diabetes (T2D), is probably attributed to the longer duration of diabetes, starting during childhood [69]. Notably, the incidence of T1D has been increasing in children in recent years and its onset has been shown to occur at a younger age [70]. Although glycemic control plays a key role in the development and progression of diabetic nephropathy [71], it has been proposed that a multitude of environmental and ethnic factors may also be involved [72, 73], [74], [75]. Furthermore, T2D, which was historically thought to represent a chronic condition of adults, has become increasingly common among children [76],[77] and recent studies have shown that up to 20% of newly diagnosed childhood onset diabetic cases are due to T2D [77], although there may be disparities across different geographical regions. Still, only few studies have investigated the risk of diabetic nephropathy among children and adolescents and data is lacking on the exact renal function loss trajectory in children with diabetes.

Childhood cancer

Improvement in the treatment of pediatric malignancies has led to higher survival rate. As a result, those who reach adulthood experience long-term therapy-related complications including CKD [78, 79]. This is related to several factors. Firstly, tumors involve the kidneys. The most common tumor involving the kidney is Wilms tumor [80]. Many of the Wilms tumor survivors exhibit subsequent renal function impairment including advanced chronic kidney disease [81]. Secondly, chemotherapy and radiation treatments have potential long-term effects. Specifically, patients treated with cisplatin, carboplatin, and ifosfamide were shown to have high prevalence of late kidney abnormalities [82]. Finally, children with any form of cancer are at risk for acute kidney injury from numerous reasons such as sepsis, drug toxicity, ischemic injury, and acute tumor lysis syndrome [83], all confer additional risk for future onset CKD.

Taken together, it seems important to maintain regular follow-up of children with past history of cancer, especially after transition into adulthood.

Lifestyle factors

Physical activity

Regular physical activity is associated with an increased quality of life and reduced morbidity and mortality in the general population as well as among patients with CKD [84]. Exclusively among adults with CKD, regular physical activity has been shown to be renoprotective for individuals across all CKD stages [84]. Furthermore, it has been shown that decreased physical activity is associated with increased mortality among patients with CKD [85].

It is well established that exercise improves different risk factors associated with the development of CKD. Physical activity protects the kidneys through several possible mechanisms which include maintenance of a healthy amount of adipose tissue, increasing insulin sensitivity and increasing bioavailable nitric oxide as well as improvement of endothelial function. [86]. The possible direct benefit of regular physical activity as protective measure for future development of CKD has been reported only in few epidemiological studies [86]. Data from the National Health and Nutrition Examination Survey suggests the low levels of physical activity contribute to future risk of CKD [87].

In children and adolescents, higher levels of physical activity were associated with better health-related quality of life [88]. Though there is limited data regarding childhood level of physical activity and future risk of kidney disease, it is highly reasonable to assume that the kidney protective effect of physical activity may delay or even prevent the development of future CKD. Nevertheless, additional future studies are needed to better understand this relationship and quantify the recommended level of physical activity.

Diet

Dietary intake is a major issue that could potentially effect individual's long-term kidney function. In a clinical trial of low fat, low carbohydrate, and Mediterranean diet among healthy adult participants, estimated GFR increased in all three intervention groups at similar magnitudes. In addition, the urinary microalbumin-to-creatinine ratio improved [89].

Several studies have shown that increased dietary salt has resulted in increased blood pressure, albuminuria, and increased filtration fraction. Based on these observations, some guidelines recommend low sodium diet as a prevention of CKD under the assumption that salt can both initiate and propagate renal injury. Among adults with CKD, there is an established association between high sodium intake (> 4.6 g\day) and subsequent decline in GFR and emergence of proteinuria. In patients without CKD, findings are inconsistent, while some studies support the association of high and moderate salt intake with future kidney damage, others do not.

In children with CKD, reducing dietary protein intake did not have a significant effect on progression of kidney disease [90], and as a result, there are no recommendations to reduce protein intake. Consequently, dietary modifications, especially restrictions, are imposed only when they are clearly needed and should be individualized. In our opinion this is also true for children without CKD.

Lastly, it should be noted that it is plausible to assume that the DASH diet (Dietary Approaches to Stop Hypertension) could have indirectly a renoprotective effect even in healthy children. This dietary approach has a positive effect on both systolic and diastolic blood pressure in the adult population [91]. It may also lead to an improvement in insulin sensitivity and play an important role in glycemic control [92].

To date, data regarding nutritional recommendations in children without CKD is lacking as a result of the paucity of evidence-based studies. Well-designed clinical trials are needed in order to define practice guidelines.

Socioeconomic status

Socioeconomic status exposures during childhood are powerful predictors of adult CKD morbidity and mortality [93]. This may be due to differences in co-morbidities, health literacy, and access to healthcare, but also poverty-associated stress and certain lifestyle-related risk factors. These early social determinants of future CKD have an important role, especially for black populations who are disproportionately disadvantaged [94].

Summary and future directions

Awareness to childhood risk factors that are potentially related to adult-onset CKD is clinically relevant in the current global CKD epidemic, as the care for patients with chronic kidney disease is also aimed at identifying at risk individuals and asymptomatic patients in early disease stages, in order to timely initiate treatments and preventive measures which can mitigate prognosis. The available published information suggests that the lifelong risk for CKD can be attributed to multiple factors which appear during childhood. These factors can be viewed under one of the following categories: genetic factors, perinatal factors, childhood kidney diseases, childhood onset of chronic conditions, and lifestyle factors (Table 2). Data is still limited on the effects of childhood physical activity, diet, and dyslipidemia on future renal function. Importantly, current data support the need for standardized monitoring for high-risk populations by pediatric and adult nephrologists as well as general primary care clinicians.

Future directions include possible early interventions that can mitigate CKD risk and its sequelae. These interventions may include as follows:

1) Screening with urine dipstick test for all children during their well-child visits
2) Adherence to the AAP guidelines for BP measurements during well-child visits [95]
3) Establishment of follow-up nephrology clinics for specific pediatric populations at risk such as preterm babies, children with cancer, children with congenital heart disease, and other at risk groups
4) Establishment of transitional nephrology clinics from childhood to early adulthood
5) Development of renal functional reserve quantification methods which can be easily used in clinical practice
6) Routine genetic newborn screening with next generation sequencing for early identification of genetic alternations related to kidney diseases later in life

Compliance with ethical standards

Conflict of Interest The authors declare no conflict of interest.

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