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CKJ Review

CKJ REVIEW

Chronic kidney disease in children: an update

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ABSTRACT

Chronic kidney disease (CKD) is a major healthcare issue worldwide. However, the prevalence of pediatric CKD has never been systematically assessed and consistent information is lacking in this population. The current definition of CKD is based on glomerular filtration rate (GFR) and the extent of albuminuria. Given the physiological age-related modification of GFR in the first years of life, the definition of CKD is challenging *per se* in the pediatric population, resulting in high risk of underdiagnosis in this population, treatment delays and untailored clinical management. The advent and spreading of massive-parallel sequencing technology has prompted a profound revision of the epidemiology and the causes of CKD in children, supporting the hypothesis that CKD is much more frequent than currently reported in children and adolescents. This acquired knowledge will eventually converge in the identification of the molecular pathways and cellular response to damage, with new specific therapeutic targets to control disease progression and clinical features of children with CKD. In this review, we will focus on recent innovations in the field of pediatric CKD and in particular those where advances in knowledge have become available in the last years, with the aim of providing a new perspective on CKD in children and adolescents.

LAY SUMMARY

Chronic kidney disease (CKD) is a devastating disease for which no cure is currently available. Lack of awareness, genetic predisposition and difficulties in measuring kidney function as a tangible sign of CKD in the pediatric population have contributed to delay the identification of effective treatments as well as the causes behind disease progression. In this review, we provide an up-to-date description of the most recent findings in terms of hereditary disorders, pathological mechanisms, novel therapeutic options and nutritional evaluations in children with CKD. We will also discuss the most recent advancements and challenges in effectively determining kidney function in young patients. Collectively, we aim to provide a novel perspective on CKD in children to boost the translation into clinical practice of the most recent discoveries.

Keywords: chronic kidney disease, genetics, innovative therapies, nutrition, pediatric

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INTRODUCTION

Chronic kidney disease (CKD) is a major healthcare issue worldwide. Recent estimates report that at least 10% of the general adult population is affected by a certain degree of CKD [1, 2] and similar projections are becoming available in children [3]. However, the prevalence of pediatric CKD has never been systematically assessed and consistent information is lacking in this population. Currently available data are derived primarily from kidney replacement therapy registries in Western countries [4, 5], thus significantly underestimating the global burden of disease. Providing patients with appropriate management and therapies along with defining the actual CKD prevalence in children represent unmet medical needs that urgently require solutions. The current definition of CKD is based on glomerular filtration rate (GFR) and the extent of albuminuria [6], which have proved to reliably predict long-term outcomes in adults [1]. Given the physiological age-related modification of GFR in the first years of life, the definition of CKD is challenging *per se* in the pediatric population. Moreover, pediatric CKD presents an additional complexity represented by an extremely variable spectrum of clinical presentations, ranging from completely silent disease (common for structural disorders) to severe kidney function impairment that markedly affects the life expectancy and quality of life of patients and their caregivers [7]. The advent and spreading of massive-parallel sequencing (MPS) technology has recently opened an interesting opportunity to promote a revision of the epidemiology of CKD in children, supporting the hypothesis that CKD is much more frequent than currently reported in children and adolescents. As in other fields of medicine, genetics is pushing our understanding of the pathomechanisms of kidney diseases. Ideally, this acquired knowledge will eventually converge in the identification of the molecular pathways and cellular response to damage, with new specific therapeutic targets to control disease progression and clinical features of children with CKD.

In this review, we will focus on recent innovations in the field of pediatric CKD and in particular those where advances in knowledge have become available in recent years: (i) the challenge of measuring kidney function and defining CKD in the pediatric population; (ii) the impact of genetics in the clinical management and in the epidemiology of pediatric CKD; (iii) the novel insights into mechanisms of CKD progression in children; (iv) the role of nutrition in balancing CKD progression and growth; and (v) the new therapeutic options for pediatric CKD. By bringing together the most recent advances in those fields, we will provide a new perspective on CKD in children and adolescents.

THE CHALLENGE OF ASSESSING KIDNEY FUNCTION IN CHILDREN

The 2012 KDIGO guidelines define CKD based on cause, GFR and albuminuria [8]. Beyond its apparent simplicity, this definition presents some challenges and pitfalls that are peculiar to the pediatric population.

GFR can be measured (mGFR) using exogenous markers by iohexol and iothalamate clearance or renal scintigraphy [9–12]. However, these investigations are costly, time-consuming and relatively difficult to perform, with limited applicability in clinical practice. Therefore, equations using serum creatinine have been developed to estimate GFR (eGFR). In the pediatric setting, the most widely used equation is the 2009 revised bedside Schwartz's formula, which estimates GFR from serum creatinine, patient's height and a constant (k) for all pediatric populations [13]. As for those used in the adult population [e.g. Modification of Diet in Renal Disease (MDRD), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), $FAS_{crea/cysC}$, etc.], this equation has some limitations. It loses accuracy in subjects with mGFR >75 mL/min/1.73 m^2 and hyperfiltration [14], potentially resulting in relevant treatment delay [15]. The small proportion of patients <5 and >15 years old in the testing cohort represented an additional flaw. To overcome these limitations, in 2021 a new equation (named CKiD U25) was validated from data of the Chronic Kidney Disease in Children study enrolling patients up to 25 years old [16]. It employs serum creatinine and cystatin C, patient age and gender without including height, therefore avoiding the issue of anthropometric data as limiting factors of the bedside Schwartz's equation. CKiD U25 proved to be more reliable in assessing CKD in adolescents and young adults in comparison with the other previously used equations [16], which were shown to underestimate (Schwartz formula) or overestimate (CKD-EPI) GFR [17]. Of note, CKiD U25 was shown to better intercept initial eGFR decline during adolescence in healthy children, making it a candidate for a promising tool for CKD screening in this population [18].

In solitary functioning kidney, renal length is considered as surrogate of kidney function in the first years of life [19]. An updated ultrasound-based kidney length normative value based on body weight and surface area in addition to age and gender was recently proposed to increase accuracy [20]. These aspects highlight the importance of linking kidney function with kidney structure and nephron endowment in young patients who may have not yet developed hypertension or albuminuria, early markers of kidney impairment. Since these patients often have "normal" values of serum creatinine and eGFR, it could be incautiously claimed that they do not present "implications for health" related to CKD. However, recent studies suggest a not negligible risk of CKD that emerges in late adolescence and middle-adulthood [21, 22]. These observations support the need to consider these patients at risk of developing CKD and to promote disease awareness to limit the number of missing diagnoses [21]. New cutting-edge research and imaging techniques (e.g. multiparametric magnetic resonance imaging, positron emission tomography, etc.) are being implemented to better define the kidney function, nephron number and hence prognosis [23–25]. Until then, surrogate indicators like prematurity, low birth weight (LBW) and pregnancy stressors will still be essential to identify children at risk of CKD [26].

The assessment of kidney function has many limitations in newborns. Serum creatinine is an unreliable marker in the first 72 h of life, as it crosses the placental barrier, mostly reflecting maternal values [27]. Cystatin C represents a valuable alternative [28]. Furthermore, in newborns GFR is physiologically <60 mL/min/1.73 m^2, reflecting organ maturation rather than kidney damage. A recent meta-analysis showed that the trend of GFR has a biphasic increase, doubling in the first 5 days of life (from 19.6 to 40.6 mL/min/1.73 m^2), with a subsequent gradual increase to about 60 mL/min/1.73 m^2 by 4 weeks of age, then reaching an asymptotically maturation by 18–24 months [29]. An updated k coefficient for Schwartz's equation and new reference intervals for serum creatinine and blood urea related to gestational age have been proposed for this group [30]. The same authors described an association between some maternal comorbidities (e.g. pre-eclampsia, diabetes, CKD, hypertension, etc.) and higher newborns' serum creatinine and urea levels suggesting that maternal conditions should be considered on kidney function evaluations in newborns and infants [30]. Preterm infants have a slower maturation of kidney function with a higher

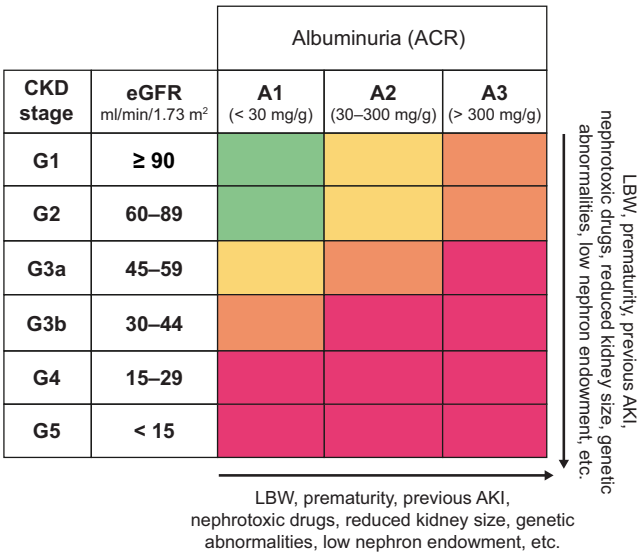


Figure 1: Staging of CKD in children and adolescents. This picture illustrates CKD definition and staging according to KDIGO guidelines. This definition is based on eGFR and proteinuria. Colors (from green to red) refer to the risk of progression toward kidney failure. Additional clinical features and events significantly increase the risk of developing CKD and staging worsening in the pediatric population. These features need to be taken into account in order to properly assess and stage CKD in children and adolescents. ACR, albumin-to-creatinine ratio.

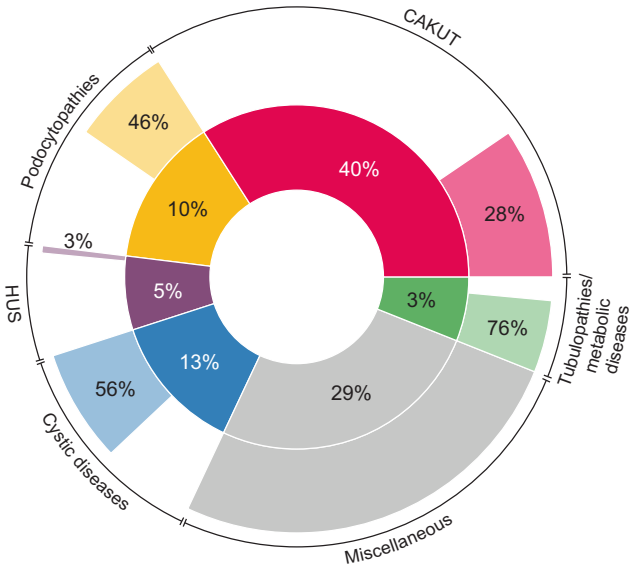


Figure 2: Causes of CKD in children and young adults and frequency of genetic forms. The inner circle represents the primary kidney disease distribution in percentage at the start of kidney replacement therapy in Europe in the pediatric population (data from ESPN/ERA-EDTA Registry, Annual Report 2018). The outer circle represents the proportion of genetic diagnosis according to each group of diseases (data from [45, 58, 62, 163–165]). HUS, hemolytic–uremic syndrome.

risk of neonatal acute kidney injury (AKI) and lifelong CKD [31–33]. In the most recent years, pediatric nephrologists and neonatologists have made significant efforts to raise awareness about neonatal AKI and to prevent its occurrence [34]. When suspecting CKD in newborn/infants, an accurate evaluation of the trend of GFR would probably allow an early identification of an altered nephron recruitment or low endowment. Moreover, cystatin C could be more accurate than serum creatinine for GFR estimation in the first month of life, especially in preterm born and very LBW neonates, with values >2 mg/dL likely suggesting AKI or reduced eGFR setting aside the need for urinary output or eGFR using serum creatinine [35].

In conclusion, although many useful tools to estimate kidney function are available in the pediatric population, physicians are called to identify the correct method for each patient (Fig. 1), and clinical features are essential for a global and accurate evaluation.

CHANGING THE LANDSCAPE OF PEDIATRIC CKD: THE ROLE OF GENETICS

The technological revolution that has been progressively replacing traditional Sanger sequencing with MPS represents the foundation of the "genomic era" in clinical medicine, including nephrology. The impressive expansion of the number of genes associated with specific kidney phenotypes (e.g. steroid-resistant nephrotic syndrome, primary tubulopathies, nephronophthisis, atypical hemolytic–uremic syndrome, etc.) promoted the introduction of genetic testing with MPS in clinical practice, with the aim of defining etiological clues underlying clinical pictures, and to inform prognosis and therapeutic management [36]. To date, more than 600 genes are listed as the cause of kidney diseases, with almost monthly updates [37, 38]. Currently available sequencing platforms allow clinicians to explore them simultaneously, with relevant implications for clinical practice [39, 40]. Pediatric nephrology represents the field where this knowledge was initially built. According to epidemiology and registry data, the primary cause of CKD and kidney failure differ in the pediatric and adult population [41, 42]. In children and young adults (i.e. younger than 25 years old) congenital anomalies of the kidney and urinary tract (CAKUT), steroid-resistant nephrotic syndrome, chronic glomerulonephritis and ciliopathies account for >70% of cases [3, 43]. These disorders show a monogenic cause in 10%–60% of cases [43–45] (Fig. 2). Since copy number variations account for an additional proportion of cases, the role of genomics in pediatric CKD can be underestimated [39, 40]. This is particularly relevant for CAKUT [46]. Variants in intronic and regulatory regions or in genes modulating chromatin organization probably represent additional sources of genetic predisposition [26]. These data have been strengthening the concept that CKD and kidney failure can be of genetic etiology in children, making genetic testing a key tool in the diagnostic pathways of patients, thus informing prognosis, treatment options and familial counseling, together with epidemiology [39].

The application of genomic strategies in pediatric patients with CKD has provided support to understanding that monogenic forms of kidney disorders are not exclusive to children. Recently, few studies explored the role of genetics in adult nephropathies and CKD [47–52], with conflicting results. Differences in diagnostic yields are due to nonuniform selection criteria, sequencing strategies [i.e. gene panels, exome sequencing (ES), etc.], bioinformatic analysis and variant prioritization. Though better performances have been obtained in cohorts of patients with specific phenotypes or diseases, genetic testing has clearly shown utility also in dissecting the cause of CKD of unknown origin (CKDu) [53, 54]. Of note, genetic testing with ES proved to have ,efficacy in detecting a monogenic cause of CKD in a large unselected population of adult patients with kidney diseases, providing a diagnostic yield of nearly 10% [52].

While disease awareness about genetic forms of CKD is certainly robust among pediatric nephrologists, how to integrate genetic testing in routine clinical practice, together with cost concerns, are still debated aspects that risk representing a bottleneck to further implementation in daily clinical practice [45, 47, 53]. As an answer to the constantly increasing demand of genetic testing in patients with CKD, organizations and healthcare systems have been trying to set up service delivery models for the optimization of genomic strategies into routine practice [55]. Although providing significantly different results, these preliminary experiences agree upon the clinical utility of genetic testing in patients with kidney diseases and CKD [49, 50, 56–60]. An economic evaluation showed that early ES is effective in diagnosing monogenic kidney disease and leads to substantial cost savings in children with glomerular disorders [49, 61]. We recently confirmed these data in a large cohort of patients with CKD, where the prospective application of a clinical workflow based on patient selection, genetic diagnosis by ES, reverse-phenotyping and multidisciplinary board discussion, provided a diagnostic rate as high as 67% irrespective of patient's age, and proved to be cost saving [62]. These observations have important implications for optimizing the use of diagnostic investigations. Future perspectives are represented by longitudinal, cross-sectional, prospective, long-term studies assessing efficacy and cost-effectiveness of genomic-first approaches to CKD. In the next future, they will include whole-genome sequencing to improve diagnostic efficacy. Preliminary results including rare kidney diseases have already been published [63].

Increasing evidence suggests that heritability of kidney function exceeds that of monogenic Mendelian traits [64], and that the genetic make-up of CKD is more complex than previously thought. Genome-wide association studies are currently used to illuminate the genetic underpinnings of complex human characteristics, such as CKD. High-frequency and low effect-size variants in *APOL1*, *UMOD*, *COL4A3* and other genes have been reported to increase the risk of developing kidney diseases and CKD [64, 65]. The combination of multiple variants in polygenic risk scores or genome-wide polygenic scores [66, 67] and their clinical utility in identifying individuals with a high genetic predisposition for CKD and in optimizing therapeutic and preventive measures is an additional active area of research [64, 68].

MECHANISMS OF CKD PROGRESSION IN CHILDREN

The mechanisms underlying CKD progression are multifactorial and only partially understood [1]. The still low disease awareness further contributes to a general lack of effort in identifying the causes behind its progression [1, 7]. The scenario is particularly complex in children and young adults where CKD results mainly from hereditary disorders, birth defects or aggressive treatments causing AKI (e.g. use of chemotherapeutic drugs). The lack of uniformity in the use and timing of nephroprotective therapy (e.g. antiproteinuric drugs) can represent additional influencing factors.

Kidney is a slowly proliferating organ with a limited capacity for regeneration. During nephrogenesis and fetal development, progenitor stem cells give rise to all the different portions of the nephron [69]. Termination of nephrogenesis around the 34th–36th gestational week in humans marks the end of new nephron endowment [70]. Premature and LBW babies frequently display incomplete kidney development and low nephron endowment [71–73]. This condition in conjunction with other risk factors (AKI or genetic predisposition) can promote CKD development at any stage [74]. Defects in nephron differentiation [75] or depletion of progenitor stem cell pool [76] account for some of the cellular mechanisms leading to CAKUT, the major contributor to CKD in children [77]. This scattered progenitor population is maintained also in the adult kidney, but its ability to replace lost cells after damage is rather limited [78], implying that the kidney has to adapt to an injury rather than fully regenerate. Despite this, children and young adults have a remarkably higher capacity to withstand kidney injury in comparison with adults [79, 80]. This is thought to be mostly due to the higher renewal capacity of progenitor cells in childhood [77] which declines over time but is impaired in patients with congenital abnormalities affecting these cells. Lost nephrons are then replaced by fibrotic tissue to maintain kidney architecture and these structural changes mark CKD development [81].

The classical view regards the glomerulus as the epicenter of kidney disease progression while tubular injury is generally considered secondary to glomerular involvement [82]. Nonetheless, diseases originating in the glomerulus account for a relatively small portion of CKD in children [83]. These patients progress more quickly to kidney failure and are generally older at disease onset when compared with children affected by other causes of CKD [84]. In contrast, diseases that primarily affect the tubulo-interstitial compartment (e.g. CAKUT, ciliopathies, tubulopathies, etc.) account for the majority of cases of CKD in children and usually show a slow progression [3]. Increasing evidence shows that damage to tubular epithelial cells (TEC) has a central role in promoting CKD progression in tubulointerstitial diseases [85, 86]. Unlike progenitor cells, TEC are terminally differentiated cells incapable of regeneration [85]. Tubulointerstitial fibrosis and CKD are triggered by injury that in tubular cells promotes cell hypertrophy via polyploidization [85, 86]. Polyploid cells can turn senescent and drive CKD progression over time [86]. Evolutionarily, polyploidization is an adaptive mechanism that allows the rapid increase of DNA content in response to an injury, without undergoing cell division [87]. Genetic or drug-induced defects in the DNA damage response can trigger polyploidization [88–95]. In children, mutations in DNA repair genes such as *FAN1* and *ERCC1* [89–91] drive tubulointerstitial fibrosis and CKD with a pathology picture of karyomegalic nephritis, characterized by massive tubulointerstitial fibrosis and the formation of enlarged nuclei in the kidneys and other tissues [89, 90, 92]. These patients experience proximal tubular dysfunction, often manifested as Fanconi's syndrome, leading to progressive kidney impairment at a young age [90]. This condition is also observed in CKD secondary to ifosfamide [94] or other drugs used to treat pediatric tumors [95] as well as viruses integrating into the genome [96, 97]. Similar to genetic mutations, these insults can affect the ability of the DNA to repair. Studies conducted between 1980 and 2010 reported that CKD affects up to 30% of children treated with ifosfamide and is dose-dependent [98–104]. The scarcity of more recent data on this subject urgently calls for data renewal due to the increased survival rates after childhood cancer [105] and the growing use of ifosfamide in children [106]. This is even more relevant when considering that ifosfamide, like cisplatin and other chemotherapy drugs, can cause AKI [104, 107] which was recognized as an important risk factor for CKD only recently [108]. Due to technical limitations in defining AKI in children, pediatric AKI is still largely underdiagnosed. Despite this, it was found to be common in pediatric intensive care units with an incidence that spans from 10% to 35% of the admitted children [109].

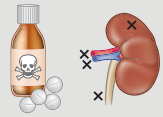
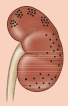
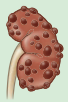
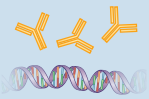
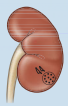
Etiology	Disease	Mechanisms	Available treatments
 Toxic (chemotherapeutics, antibiotics, NSAIDs) Glomerulonephritis Ischemia (dehydration, etc), obstruction	AKI	 Polyploidy (including karyomegalic nephritis, TEC senescence)	Stop/avoid insult, supportive measures, dialysis
 Toxic (chemotherapeutics) Immunologic	Tubulointerstitial diseases	 Polyploidy (including karyomegalic nephritis, TEC senescence)	Stop/avoid insult, steroids, supportive measures, dialysis
 Genetic Environmental factors (nutritional deficit in pregnancy, etc.)	CAKUT	 Low nephron endowment	Reduction of nephron overload (RAS blockers, SGLT2-inhibitors)
 Genetic	Ciliopathies	 Tubulointerstitial structural abnormalities	Supportive measures, dialysis
 Genetic Immunologic	Glomerulopathies	 Glomerular polyploidy, structural/functional abnormalities	Supportive measures, immunosuppressors, dialysis

Figure 3: Mechanisms of CKD progression in children. Scheme summarizing the main mechanisms of pediatric CKD progression and available treatments according to the etiology of CKD. NSAIDs, non-steroidal anti-inflammatory drugs; TEC, tubular epithelial cell; RAS, renin–angiotensin system.

Collectively, chemotherapy and tubulointerstitial damage secondary to nephrotoxic drugs, AKI and congenital conditions can cause CKD in children [95] via TEC dysfunction suggesting that TEC may have a more prominent role in many different forms of CKD than previously thought, especially in children (Fig. 3).

KIDNEY FUNCTION AND GROWTH IN CKD PATIENTS: IS NUTRITION THE KEY?

CKD is the result of the imbalance between the functional capacity of the kidney and the metabolic needs of the body. A peculiar feature of the pediatric population is that this equation is unstable by definition. In growing children metabolic requirements substantially increase with time, while at the same time in progressive CKD the kidney's capacity to handle metabolic load declines. From a clinical perspective, this mismatch can result in growth failure [110, 111]. The degree of growth impairment increases as GFR declines [3, 112] and is linked to the other CKD features: anemia, metabolic acidosis, electrolytes anomalies, mineral-bone disorders, sexual hormones dysregulation and malnutrition [112].

In patients with CKD, different compensatory mechanisms are established to offset progressive loss of nephron mass. Studies in preterm and LBW infants suggest that hyperfiltration of remaining nephrons is a key adaptive mechanism to support residual kidney function and to some extent growth [113, 114]. Unfortunately, the tradeoff of these strategies is progressive CKD development [113]. Whether poor growth is merely a consequence of CKD or even represents itself a factor promoting progression, which is the cost-to-benefit ratio of pursuing growth in children with CKD and which is the role of nutrition in growth, in CKD and in CKD progression are still open questions. Final adult height in CKD pediatric patients is significantly reduced compared with the healthy population [115]. All these aspects contribute to creating a gap between children and adolescents affected by CKD and their peers, influencing the emotional, psychological and social state of these patients [116]. In this view, CKD should be considered as a "social" disease. Along with other different disease manifestations, growth impairment severely impacts on children's quality of life [116]. In the CKD population, growth is influenced by nutrition more than the growth hormone–IGF-I axis [3, 110]. Patients frequently receive a reduced intake of nutrients due to the limits imposed by CKD and by restrictive "renal diet" [110, 117], which lead to an inadequate energy reserve with respect to the body requests. Drugs, loss of appetite due to increased anorectic hormones and taste alterations further contribute to poor nutrition [112, 118]. On the other hand, patients experience altered absorption of nutrients due to increased uremic toxins and bowel inflammation [119, 120]. For these reasons nutritional plans should be tailored to the patient's needs: age, gender, race, nutritional and growth parameters, degree of physical activity, cause of CKD (i.e. presence of particular electrolyte imbalance, presence of residual diuresis) are relevant [110, 117]. The 2009 KDOQI Clinical Practice Guideline for Nutrition in Children with CKD and The Clinical Practice Recommendations from the Pediatric Renal Nutrition Task Force published in 2019 suggested that the initial prescription for protein intake should be at the upper end in patient with CKD to support growth and modulated based on urea levels and growth [118, 121]. To this end, the proposal to revise the use of protein restriction recently came to the stage. Recommendations on a low protein diet in the adult population were based on only few studies with weak evidence of actual effects on slowing the CKD progression [122]. According to this, it may be more important

Table 1: Pipeline clinical trials in pediatric CKD patients.

Clinical target	Mechanism	Drug	Trial phase	Trial identifier
Bone metabolism	Calcium-sensing receptor agonist	Cinacalcet	III	NCT02138838
Bone metabolism	Calcium-sensing receptor agonist	Cinacalcet	III	NCT01290029
Bone metabolism	Calcium-sensing receptor agonist	Cinacalcet	II	NCT01439867
Bone metabolism	Calcium-sensing receptor agonist	Cinacalcet	III	NCT02341417
Bone metabolism	Calcium-sensing receptor agonist	Etelcalcetide	III	NCT03633708
Bone metabolism	Calcium-sensing receptor agonist	Etelcalcetide	I	NCT02833857
Bone metabolism	Calcium-sensing receptor agonist	Etelcalcetide	III	NCT03969329
Anemia	HIF2 inhibitor	Vadadustat	III	NCT05082571
Anemia	HIF2 inhibitor	Vadadustat	III	NCT05082584
Anemia	HIF2 inhibitor	Roxadustat	III	NCT04925011
Hypertension	MRAs	Finerenone	III	NCT05196035
Hypertension	MRAs	Finerenone	III	NCT05457283
Bone metabolism	Phosphate binder	Lanthanum Carbonate	II	NCT01696279
Hyperkalemia	Potassium binder	Patiromer	II	NCT03087058
Inflammation	Triterpenoid	Bardoxolone	III	NCT03749447

to take into account the protein kind rather than the amount, as not all proteins produce the same amount of acids to be neutralized [122]. Given the issue of increased risk of growth impairment, such reevaluation would have a great impact on the clinical management of pediatric CKD patients.

Enteral nutrition is recommended to support and improve the nutritional status of patients with low oral caloric intake or in patients without weight improvement despite the optimization of the nutritional scheme [123, 124]. The first 6 months of life are critical for growth and can be particularly affected by malnutrition requiring a more aggressive nutritional approach [112, 123, 124].

The role of a plant-based diet in the management of CKD has been consolidating in recent years [125, 126]. Interventional trials in adults have shown benefits in controlling metabolic acidosis and in slowing CKD progression. Pleiotropic benefits on blood pressure, intestinal permeability and gut dysbiosis as well as reducing the medications burden have been suggested [119, 125–127]. Although promising, studies on the ability of vegetarian diets to satisfy nutritional needs and optimize growth in pediatric patients with CKD are lacking.

In conclusion, nutrition could represent a tool for slowing down CKD progression, reducing the use of drugs and improving growth in pediatric patients with CKD. However, a personalized approach should be tailored to each patient to ensure the appropriate balance among all clinical needs.

NEW THERAPEUTIC PERSPECTIVES FOR PEDIATRIC CKD

Given the burden of CKD, new therapies allowing better clinical management and slowing disease progression are needed. The most recent years have been characterized by excitement for new therapeutic options that have just entered clinical practice for the adult patients. Some of them will be tested in pediatric patients (Table 1) [128].

New therapeutic options became available for CKD-related anemia. Large trials using hypoxia-inducible factor 2 prolyl hydroxylase inhibitors (HIF2-PHIs; roxadustat, vadadustat and daprodustat) were completed in adult patients with positive results [129–136]. These compounds act by slowing the degradation of HIFs, thus enhancing the production of endogenous erythropoietin. They also seem to improve the absorption and use of iron from food. Roxadustat is currently being tested in a clinical trial in pediatric CKD patients (NCT04925011) [137]. Although the results are not yet available, these new drugs will constitute a further tool to address resistance to erythropoiesis-stimulating agents in children. However, long-term safety still remains to be assessed.

In children with CKD, the treatment of calcium/phosphorus axis dysfunction is essential as it markedly affects growth. The constitutive activation of the parathyroid hormone (PTH; i.e. secondary hyperparathyroidism) already occurs in the intermediate stages of CKD [138, 139]. Therefore, the timing of action is narrow as the lost growth potential of first years is not recoverable [140]. Calcimimetics are a class of drugs that lower the threshold for calcium-sensing receptors' activation by extracellular calcium ions, thus reducing PTH release from parathyroid cells [141]. These drugs are already in use in adult CKD patients on dialysis. Recently, a small number of sponsored trials has been completed using cinacalcet, available for children over 3 years old on dialysis with hyperparathyroidism not controlled with standard-of-care therapy. First results showed the reduction of PTH level in up to 57.1% of enrolled patients [142]. Etelcalcetide is under study in a phase III trial (NCT03633708) [143]. Additional drugs acting on calcium metabolism have been proposed to enter into use for the pediatric population in the next few years [139].

Mineralocorticoid receptor antagonists (MRA) are used for treating low-renin or refractory hypertension [144, 145]. Previous MRA antagonists, spironolactone and eplerenone, did not receive wider use in CKD patients mainly for safety concerns related to hyperkalemia [146] and for sex hormone–related adverse events due to affinity for progesterone and androgen receptors [145]. Recently, a new highly selective, non-steroidal MRA, finerenone, has been shown to be effective in improving renal outcome in patients with diabetic CKD in two trials: FIDELIO-DKD [147] and FIGARO-DKD [148]. These trials enrolled mainly albuminuric patients, therefore data on the efficacy in non-albuminuric patients with diabetic and nondiabetic kidney disease are still missing. The FIND-CKD study (NCT05047263) investigating finerenone in adult nondiabetic CKD is ongoing [149]. Interestingly, finerenone is currently being tested in two phase III open-label trials (FIONA, NCT05196035; FIONA OLE, NCT05457283) for pediatric CKD patients [149–151].

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) were originally designed for diabetic patients with CKD and then were found to be protective even in the adult population with nondiabetic CKD [152]. They reduced the risk of kidney disease progression up to 37% (relative risk 0.63, 95% confidence interval 0.58–0.69) and improved kidney and cardiovascular outcomes, making them a game-changer historically comparable only to renin–angiotensin system inhibitors [153]. The long-term protective mechanisms are still being elucidated, however it is thought that in the kidney they may act mainly through the inhibition of the tubuloglomerular feedback, which is dysfunctional in CKD, reducing hyperfiltration [154, 155]. Other proposed mechanisms are the systemic metabolic reset linked to nutrient deprivation signaling with its cytoprotective effects and reduction of mitochondrial oxidative stress in proximal tubular cells [155]. Interestingly, a recent analysis showed that SGLT2i can provide a substantial reduction in costs related to CKD, mainly driven by the reduction in the outcomes and by the cardio- and nephroprotective effects [156–159]. Furthermore, the issue of cost-effectiveness is especially relevant in children. Recent pilot studies suggested that SGLT2i are effective in reducing proteinuria in children with CKD [160, 161]. Despite these big premises, up to now no trials have been registered for pediatric CKD patients [152].

In recent years new drugs to slow CKD progression have entered into the nephrologist's clinical practice. However the efforts for bringing them into daily practice probably should be increased by pediatric nephrologists, considering the lower number of clinical trials registered for CKD when compared with that of other conditions such as heart failure and the low number of trials resulting in effective publication [162].

CONCLUSIONS

The heterogeneity of causes and the lack of complete understanding of mechanisms underlying CKD in children are reflected in the absence of effective treatments to slow CKD disease progression and prolong patient survival, with profound implications for morbidity and mortality. Given the economical and organizational concerns related to CKD, any intervention potentially leading to preventing its progression toward kidney failure is crucial and would be required to appropriately allocate resources [7]. The main step on this path is the identification and correct disease classification, which is still difficult given the peculiarities of pediatric patients. This can only be successfully achieved by acting on multiple fronts: (i) promoting disease awareness ensuring a correct and timely identification of pediatric patients with CKD; (ii) incorporating cutting-edge technologies in diagnostic pathways; (iii) understanding disease progression mechanisms; (iv) balancing out the need to promote growth and keep CKD under control; and (v) incorporating newly available treatments for CKD resulting from either translation of results from clinical trials in adults or as directly designed for the pediatric CKD population. Only by synergistically combining these fronts together will effectively acting on preventing CKD and its devastating consequences in the pediatric population become routine clinical practice.

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DATA AVAILABILITY STATEMENT

No new data were generated or analysed in support of this research.

CONFLICT OF INTEREST STATEMENT

P.R. is member of the *CKJ* editorial board. The other authors have no conflict of interest.

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