

Revisiting the Chronic Renal Disease in Pediatric Patients

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ABSTRACT

This paper aims to review the diagnosis, epidemiological data, etiology, pathophysiology and progression of Chronic Kidney Disease (CKD), with emphasis on pediatric patients. CKD is defined as a group of structural and functional kidney abnormalities observed for more than three months, which affects patient's health. CKD prevalence in children is lower than in adults, but is associated to cardiovascular diseases and has high mortality and morbidity rates. CKD-affected children have alterations in physical and psychological development, growth retardation and muscle weakness, among other complications which decrease patients' quality of life. The main causes of CKD in children are congenital anomalies of the kidney and urinary tract, and primary glomerulopathy, especially focal segmental glomerulosclerosis. Some conditions contribute to CKD progression, such as responsiveness to treatment. The knowledge of the pathophysiology of CKD and disease progression mechanisms is important for the early treatment and to predict the clinical evolution, aiming to provide counseling to families and to slow the progression of kidney disease to an end stage.

Keywords: chronic kidney disease; pediatrics; etiology; prevalence; progression.

INTRODUCTION

Chronic kidney disease (CKD) is defined according to the presence of structural and functional abnormalities of the kidneys for more than three months, with implications for the patient health. [1] CKD lesions are slow, progressive and irreversible, and can culminate in the development of the end stage of kidney disease (ESKD), in which kidneys stop working and the maintenance of life depends on renal therapies instead. [1,2]

CKD is a serious worldwide public health problem. Its prevalence ranges from 8 to 16% of the population, and is sharply increasing, with strong possibility of

reaching epidemic proportions in the incoming years, impacting the cost of healthcare systems. It is estimated that the number of ESKD-treating patients in the world was of 3.2 million by the end of 2013. From these patients, around 2.5 million need dialysis and 678.000 demanded renal transplant. [3-7]

CKD classification is based on its origin, on the degree of glomerular filtration rate reduction (GFR), which is used to evaluate the functional capacity of the kidneys, and on albuminuria levels. [1,2,8] CKD complications include mortality by cardiovascular reasons, progression of kidney disease, acute kidney injury,

cognitive decline, anemia, bone and mineral disorders and fractures. [7] CKD in the pediatric population is relevant given that it is associated to the aforementioned mortalities and morbidities causes, and also to growth retardation, muscle weakness, amidst other that decreases quality of life. [3,9] These children face difficulties in social life due to specific dietary needs, compliance to dialysis, the constant use of medications and hospitalization resulting from frequent clinical interventions. [9-11]

ESKD development threatens life expectancy of patients. Mortality rates for children on dialysis can be from 30 to 150 times higher than rates for healthy children. The life expectancy for a child from 0 to 14 years on dialysis is only 20 years, with high risk of developing cardiovascular diseases such as hypertension, what emphasizes the need of encouraging primary prevention, early diagnosis and continuous care. [12-14]

Early prevention measures in CKD in pediatric population are essential to slow its progression and impact favourably on morbidity and mortality. The knowledge of

the pathophysiology, associated complications and mechanisms of CKD progression are important for the early diagnosis, prognosis and approach to sick children and their families. [12-14] In this context, this review aimed to present recent data about the diagnosis, epidemiology, etiology and pathophysiology of CKD in the pediatric population.

CKD Diagnosis and Staging

The diagnosis of CKD is performed when there are structural and functional abnormalities of the kidneys or with GFR lower than 60mL/min/1.73m², for a period superior to three months, with implications for the patient health. The end-stage kidney disease (ESKD) is characterized by GFR levels lower than 15mL/min/1.73m², and renal replacement therapies such as dialysis or transplantation are necessary for life. [1,6,15,16] Transplant is the best therapeutic option for patients with chronic renal failure, even before starting dialysis that promotes a greater survival rate. [17] CKD is classified in stages, according to the GFR, as shown in table 1.

Table1: GFR categories in CKD*

GFR category	Terms	GFR (mL/min/1.73 m ²)
1	Normal or high	≥90
2	Mildly decreased GFR	60-89
3a	Mildly to moderately decreased GFR	45-59
3b	Moderately to severely decreased GFR	30-44
4	Severely decreased GFR	15-29
5	Kidney failure	≤15

*GFR: glomerular filtration rate. CKD: Chronic Kidney Disease. Related to young adult levels. In the absence of evidence of kidney damage, neither GFR category 1 nor 2 fulfill the criteria for CKD.KDIGO, 2013. [1]

Further, GFR classification can be based also on CKD origin and on the degree of albuminuria. [1,18] Kidney damage is defined based on structural or functional changes of kidney, followed or not by GFR reduction. It may show up through changes in the composition of blood and urine (proteinuria, albuminuria, alterations in urinary sediments), pathological changes in the imaging diagnosis and genetic disorders. [1,15,18]

Amidst pediatric patients at risk of developing CKD, we can mention those with family history of polycystic kidney disease or other genetic kidney diseases,

low birth weight, history of renal failure by perinatal hypoxia, renal hypoplasia or dysplasia, urological disorders, particularly obstructive uropathies, subsequent vesicoureteral reflux associated to repeated urinary tract infections and renal scarring, history of nephrotic syndrome, acute nephritis, hemolytic uremic syndrome, diabetes mellitus, renal artery hypertension or renal venous thrombosis in the neonatal period. [19]

CKD diagnosis in children through GFR and early classification of kidney disease is complex, mainly due to the difficulties in accurately determining GFR

in children, including newborns with structural abnormalities of the kidney (the complexity of the 24-hour urine collection and difficulty of urinary sphincter control). [3,4]

As the GFR cannot be easily measured in most clinical or research environments, equations based on filtering markers such as serum creatinine and cystatin C are used to estimate GFR. Several formulas of GFR estimation are based on the relation of plasma creatinine and GFR. [20]

One of the most employed equations to estimate the glomerular filtration in pediatric population is the formula of Schwartz: $GFR = (k \times h) / CCr$, in which GFR is estimated in mL/min/1.73 m², where h corresponds to the height (cm), k is an empirical constant and CCr is the plasma concentration of creatinine (mg/dL). The value of the constant k depends on the age, gender and the laboratory method for determination of plasma creatinine. [8,21,22] When creatinine is determined by the Jaffé colorimetric method and the following values for the constant K are used: 0.45 for newborns to term until the first year of life; 0.55 for children of both gender and female adolescents, and 0.7 for male adolescents. [8,22] However, when the creatinine is measured by mass spectrometry, the use of the constant K value of 0.413 is recommended for children over one year old, regardless of sex, i.e., the modified Schwartz formula. [21]

It is noteworthy that the detection of GFR values lower than 60mL/min/1.73 m² for a period of three months or more is not considered a diagnostic criterion of CKD in children under two years of age, once the GFR varies physiologically according to age, gender and body weight, and rises gradually from birth, reaching values considered normal for adults only after two years old. [3]

CKD Prevalence in Pediatrics

The currently available epidemiological data on the prevalence and incidence of CKD in the pediatric

population are scarce, inaccurate and flawed due to methodological differences between the various sources. Overall, the prevalence in children is smaller in relation to adults and these data refer to the most advanced stages of the disease, when the kids are already on dialysis or post-transplant. [3,4] Most children with change in kidney function reaches the ESKD above the children age, and therefore are not included in these records that, consequently, provide incomplete data. [23]

The fact that many children are asymptomatic in the early stages of CKD also contributes to the lack of information on prevalence. [4] However, more in-depth knowledge about this population is important, since the early stages of kidney injury are potentially more susceptible to therapeutic interventions that modify the course of the disease and prevent the progression to ESKD. [23]

The prevalence of ESKD in U.S.A. children was estimated at 82 patients per million of aged compatible population. [4] In Europe, the average incidence of preterminal CKD from 1995 to 2000 was of 12.1 cases/year/million people, with prevalence of 74.7 cases/million people under 20 years. [23] In France, between 1975 and 1990, the incidence rate of CKD in stages 3 and 4 was of around 7.5 cases/million people under 16 years. The prevalence of ESKD ranged from 29.4 and 54 per million in this population with compatible age. [24] In Brazil, from the 34.161 new cases of dialysis in the year of 2012, 0.4% had up to 12 years old and 5.6% ranged from 13 to 18 years old. [25] The comparison between CKD epidemiology studies in pediatric population conducted in different geographic regions is complicated due to methodological differences in case definitions and in classification of the disease. [23]

CKD Etiologies

The etiology of CKD differs in children when compared to adults. While diabetes and hypertension is the main responsible for the occurrence of the disease

in adults, the congenital causes have higher percentage in children. [3,4,7,26] Amidst the main, are the congenital anomalies of the kidneys and urinary tract (CAKUT), followed by primary nephropathy, which add up to about two-thirds of cases of Pediatric CKD in developed countries. [3,4,23]

According to the data of the *North American Pediatric Renal Transplant Cooperative Study* in 2008, the congenital causes of ESKD, including anomalies (48%) and hereditary kidney diseases (10%), were the most common etiologies of Pediatric CKD in the U.S.A. Glomerular diseases corresponded to 14% of cases. [3]

In Europe, the proportion of CAKUT was of approximately 58%. In the Italian population, the main causes of CKD were hypoplasia/dysplasia associated to urinary tract malformations (53.6%) and hypoplasia/dysplasia (13.9%) alone, while the glomerular diseases accounted for only 6.8% of cases. [3,23]

In several countries of Latin America, from 1458 patients under 21 years who received kidney transplant from 2004 to 2008, the etiology and the percentage of cases that resulted in kidney transplant were: reflux nephropathy/uropathy (27%), glomerular diseases (24%), hypoplasia/dysplasia (11%), of congenital/inherited causes (5%), vascular diseases (5%) and of unknown etiology (19%). Structural defects such as obstructive uropathy, reflux nephropathy and hypoplasia/dysplasia represented the largest proportion (38%) of primary causes of CKD in children under five years. [27]

The causes of CKD vary in the world according to ethnicity and socioeconomic conditions. In developing countries there is a predominance of infectious or acquired causes. Chronic glomerular diseases are the main causes of CKD in children in India, Southeast Asia, Latin America, the Caribbean and Sub-Saharan Africa regions, with prevalence ranging from 30 to 60%. These proportions may be related to substantial prevalence in these countries of viral, bacterial and

parasitic infections that affect the kidneys. [3]

Differences in reports of pediatric CKD among the various geographical regions of the world can be attributed to distinct genetic, environmental and cultural characteristics. [4] The causes of pediatric CKD vary with age, with prevalence of structural causes in younger patients and of glomerular diseases in patients over 12 years. [3,23,27]

Congenital Anomalies of the Kidney and the Urinary Tract (CAKUT)

CAKUT are amidst the leading causes of CKD in the pediatric population and amidst the most frequently observed malformations in human beings. [28] These anomalies include structural and functional malformations in the renal system, kidneys, ureters, bladder and urethra, such as renal agenesis, renal dysplasia, *multicystic dysplastic kidney*, duplication of the collector system, polycystic kidney, posterior urethra valve, ureteropelvic junction obstruction, hydronephrosis, and vesicoureteral reflux megareter. [29,30] These occur in every 1:500 live births and are responsible for approximately 1 death for every 2000 births. Approximately 89% of CAKUT are detected through ultrasound during the prenatal period, [29] which has improved the survival rate of newborns with such changes. [31]

The prognosis of the CAKUT is variable and depends on the presence of obstructive uropathy. [32] It is estimated that two-thirds of patients with posterior urethral valve will develop CKD and that 11 to 51% progress to ESKD until adolescence. [33]

Most of the CAKUT are isolated malformations, but genetic influences are likely. Around 10% of close relatives of CAKUT patients also have kidney abnormalities, albeit they are often asymptomatic, what contributes to underestimate the frequency of family CAKUT. [28,29,34]

The structural abnormalities present in patients with CAKUT may originate from problems during nephrogenesis. It is known

that a complex network of genes mediates the development and differentiation of kidneys during the embryonic period. Among these mediators encoded in these genes are transcription factors, cell adhesion molecules, growth factors, cell polarity molecules and the renin-angiotensin system. Some genetic alterations in this context have been described, such as the association of polymorphisms in genes BMP4, PAX2 and AGTR2 to different phenotypes of CAKUT. The final phenotype depends on modification factors present in the intrauterine environment, such as gestational diabetes, maternal diet and drugs acting on the renin-angiotensin system. [35-38] Environmental factors present before or during pregnancy are also relevant to the occurrence of CAKUT. Not all patients with the same genotype develop malformations, and the same genotype has different stages of kidney disease, suggesting the relevance in the etiology. [29]

Glomerular Diseases

Glomerular Diseases are acquired CKD causes in adults and children, and include the primary or secondary Nephrotic Syndrome (NS). [39-41] Renal diseases referred as NS are characterized by subacute massive proteinuria, hypoalbuminemia and edema, as well as dyslipidemia and lipiduria. The presence of haematuria and hypertension is less common and is associated to the clinical forms of worse prognosis. In some patients, oliguria and transitional GFR decline may happen during exacerbation periods of the disease. [40,41]

In adults, the secondary NS is more frequently detected, and is a result of genetic alterations, metabolic diseases, infections, drug use, allergic disorders, autoimmune diseases and neoplasia. [39,41,42] In children, the primary idiopathic NS is the most frequent glomerular disease, with an estimated prevalence of 16 cases for every 100.000 children, and usually follows changes that affect the glomerular filtration barrier. The NS diagnosis is performed using clinical and laboratory criteria for histological analysis of renal biopsy. [42] The

primary NS presents two most frequent histological forms, which are the minimal change nephrotic syndrome (MCNS) and focal segmental glomerulosclerosis (FSGS). Other alterations comprise membranous glomerulonephritis, membranoproliferative glomerulonephritis and mesangial IgA glomerulonephritis. [39,41,43] The main factor for the development of predictive primary NS is not the histologic diagnosis, but the response of patients to the treatment with corticosteroids. Children with NS resistant to corticotherapy have much higher chances of developing ESKD compared to responsive. [39]

Minimal change nephrotic syndrome (MCNS)

It is the most common cause of NS in children. A Chinese study conducted in the period of 1989 to 2012 on pediatric renal biopsies examined 1579 patients and observed that 24.8% of children with primary Glomerulonephritis presented MCNS, what corresponded to 14.9% of all cases of CKD in which biopsy was performed. [44] The pathophysiology of MCNS is not yet well understood, but it is possibly resulting from changes in T cells with involvement of the podocytes, cells present in glomerular basement membrane, and exacerbated local release of cytokines. [40] Optical microscopy cannot detect glomerular changes in patients with MCNS. In electron microscopy, the fusion of the processes and discrete cell proliferation chooses to mesangial can be observed. Because the majority of children with MCNS respond well to therapy with corticosteroids, they are frequently not subject to renal biopsy, and thus this diagnosis is rarely confirmed by histological findings. [39,41]

Focal Segmental Glomerulosclerosis (FSGS)

This applies to the presence of lesions in only some of the glomeruli (focal) and in just a few portions of affected glomeruli clusters (segmental) in renal biopsies. FSGS is characterized by marked proteinuria and often poorly responsive to

corticotherapy. The diagnosis is based on histological detection of glomerular sclerosis and glomerular tuft hyalinization. From 7 to 15% of children with idiopathic NS are diagnosed with FSGS, which evolves with progressive loss of renal function, leading to ESKD in 25 to 30% of cases in 5 years, and from 30 to 40% after 10 years of evolution. [45,46] The primary defect in FSGS lies in the filtration glomerulus barrier injury, resulting in loss of selective permeability and detection of macromolecules in urine. [47,48] All FSGS forms share injury and depletion of podocytes, which are correlated to the extent of glomerular sclerosis and may arise from genetic causes or of changes in the local immune response to different stimuli. [43,47,48] In about two-thirds of the cases of primary FSGS, which show up in the first year of life, there is an association to genetic alterations. [43] Genetic heterogeneity of FSGS family forms and the wide variety of clinical forms between the carriers of mutations demonstrate the complexity of this phenotype. [49] On the other hand, there are cases in which the disease occurs in the absence of known genetic disorders and cases in which proteinuria recurrence is observed in a few hours or days after renal transplantation. [50] The primary FSGS has also been attributed to the presence of a circulating factor, able to increase the permeability of the glomerular filtration barrier. The candidates for this circulating factor include the cytokine 1 (similar to cardiotrophin), hemopexin, angiopoietin-like 4-(secreted by podocytes) and the soluble urokinase receptor (suPAR). [40,50,51] The factors that are mostly associated with a worse prognosis include the presence of interstitial fibrosis, increased serum creatinine and proteinuria. Virtually, all patients with massive proteinuria and FSGS progresses to CKD in five years. [45,47,49]

CKD Progression Factors and Clinical Management

The progression of early stages of CKD is quite variable, unpredictable, and may be associated with the underlying

disease, severity of initial lesion and presence of additional risk factors. [3] Patients respond to standard therapy with corticosteroids have an excellent long-term prognosis, and rarely evolve to ESKD. [14,39]

Children with birth defects suffer slower progression to ESKD than those with glomerular diseases and, therefore, there is a smaller proportion of hypodysplasia and subsequent management in ESKD population when compared to the early stages of CKD. [3,14,52] Primary glomerular diseases have independent association with progression to ESKD, and the average time of renal survival is lower compared to other primary renal diseases. [53] Patients with FSGS have an average time of faster progression to ESKD than other etiologies [54]

Puberty and the onset of post-pubescent period appear to be critical for patients with impaired renal function, regardless of the initial degree of dysfunction. CKD progression rate can rise in this period, with acute decline in renal survival. [23] The causes include blood pressure elevation with imbalance between residual renal mass, greater filtration needs during rapid changes in body size, and changes in endocrine Physiology. [3,23]

The presence of proteinuria is related to high blood pressure within the progression of CKD in children. [55] Beyond being a consequence of CKD, proteinuria contributes to the progression of renal injury. It is known that accumulated proteins in the tubular lumen can trigger inflammation and sclerosis, promoting structural injury and interstitial disease progression. The remission of proteinuria by the treatment raises the long-term renal survival and indicates favorable prognosis. [14,55]

GFR reduction is related to elevated values of protein/creatinine in urine. [14,56] In the pediatric population, progression to ESKD is inversely proportional to the creatinine clearance, regardless of underlying kidney disease and its additional risk factors. [4,23]

The progression of CKD is also influenced by several risk factors, which comprise factors modified by therapeutic interventions like anemia, hypoalbuminemia, hyperphosphatemia, hypocalcemia and inadequate growth, and non-modifiable factors like genetic traits, gender, age, and CKD primary cause and its stage at the time of diagnosis. [4,54] Childhood obesity contributes to the progression of CKD due to its association to hypertension, albuminuria and dyslipidemias. [4,14] Low weight at birth is followed by a smaller number of nephrons, what can also predispose the individual to hypertension and renal disease throughout his life. [3] Beyond biological influences, socioeconomic circumstances may play a significant role in health and wellbeing of children with CKD. [57]

Children with CKD go through several physical and psychological complications. Besides reduced life expectancy, they are confronted with different health and social changes, including stunted growth, growth deficit, low self-esteem, behavioral and learning issues, and delayed development of motor skills. [57] Children who survive to ESKD have worse health-related quality of life, and find difficulties in employment and independence processes, when compared to the general population. [54]

The identification of treatments that can slow CKD progression is necessary, [54] and the understanding of how to deal with the causes of mortality and morbidity in children with CKD requires information concerning risk factors that lead to adverse results. [57] For clinical management, the early follow up by a specialized team is recommended, previously to the need of dialysis. The establishment of interdisciplinary CKD specialized teams can contribute for improving quality of life and survival of patients. In pre-dialysis phase, depleting kidney function factors can be controlled by adequate clinical approach of nutrition, anemia, metabolic and acid-basic disorders, as well as supporting programs

for patients and their families ensure of adequate vascular access and an indication of renal function replacement therapy for an adequate time. [9,58]

CONCLUSION

Pediatric CKD has inherent significant morbidity and mortality, and also due to other factors that compromise the quality of life of children. The main causes of CKD in the pediatric population are also primary glomerular lesions and malformations. CKD progression depends on factors like the cause of the disease, response to treatments, obesity, proteinuria and dyslipidemias. Monitoring CKD in children should address not only the primary kidney disease, but the varied extra-renal manifestations of CKD that complicate the disease. Dialysis and kidney transplant, the main treatments for ESKD, feature very high costs for the patients. Therefore, the outcomes of CKD and quality of life of children essentially depends on social status and access to health services, in order to slow the progression of the disease.

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