

A Review of Pediatric Chronic Kidney Disease

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Key Words

Pediatric · Chronic kidney disease · Review

Abstract

Chronic kidney disease is complex in both adults and children, but the disease is far from the same between these populations. Here we review the marked differences in etiology, comorbidities, impact of disease on growth and quality of life, issues unique to adolescents and transitions to adult care, and special considerations of congenital kidney and urinary tract anomalies for transplantation.

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Background

Children with chronic kidney disease (CKD) face life-long increases in morbidity, mortality, and decreased quality of life (QOL). Significant effort has been focused recently on standardizing definitions and guidelines for CKD and management (NKF-KDOQI), describing the characteristics of pediatric patients on renal replacement therapy (RRT) (NAPRTCS), and characterizing CKD morbidity in children (CKiD Initiative). Despite the improved understanding of pediatric CKD and end stage renal disease (ESRD) that these efforts have provided, more research is required to improve outcomes in these children.

Epidemiology

Pediatric incidence of ESRD has been stable over the past 30 years worldwide, but prevalence has increased along with incidence of dialysis and renal transplant recipients [1, 2]. The median incidence of RRT in children less than 20 years old worldwide was approximately 9 per million of the age-related population (pmarp) in 2008, with the United States median higher at 15.5 pmarp [3]. The prevalence of RRT was also higher in the United States compared to that in developed countries with 85 vs. 65 pmarp, respectively. Race is differentially affected by region, with black children having 2-fold greater incidence of ESRD vs. white children in the United States. Adolescents also have a higher incidence of RRT than other age groups worldwide, with the United States much higher than Western Europe in both the 0–14 and 15–19 age groups.

According to the most recent North American Pediatric Renal Trials and Collaborative Studies Dialysis Report (NAPRTCS) [4], the youngest pediatric patients have the worst survival at 12, 24, and 36 months following dialysis initiation. Five-year survival probability is 89% for patients initiating ESRD treatment according to US Renal Data Surveillance Report [5], and mortality rate is 30 times higher than healthy children [3]. Conversely, adults have an astounding rate of expected mortality of 90% by 10 years on dialysis [5]. Cardiopulmonary death was the

most common cause cited in children, followed by infection.

A crucial difference between adult and pediatric ESRD is the etiology of CKD. Adult CKD is predominately diabetic nephropathy, hypertension, and autosomal dominant polycystic kidney disease. The top cause of pediatric CKD in registries is congenital anomalies of the kidney and urinary tract (CAKUT) at approximately 50%, followed by hereditary nephropathies and glomerulonephritis [3]. Etiology of CKD varies by age and race, with children younger than 12 years more likely to have CAKUT, and of glomerular-based disease focal segmental glomerulosclerosis is more likely in black adolescents. Obesity in children is a new problem worldwide, and recent studies [6, 7] have identified early kidney dysfunction and risk for CKD in these children. In addition, infants of low birth weight and small for gestational age have an increased risk of developing ESRD in adolescence [8, 9]. As the pediatric obesity problem rises and the low birth weight population ages, we may encounter a potential shift in the epidemiology of pediatric CKD.

Complications of CKD

Growth and Nutrition

Growth in childhood involves a balance of nutritional, metabolic, and endocrine homeostatic processes. CKD, especially if it develops early in life, leads to significant height stunting and disproportionate growth failure. Remarkably, the height deficit begins as early as the first postnatal months, with a cumulative height deficit of -3 standard deviations by 3 years of age [10]. Infants with congenital CKD can have polyuria, salt-losing nephropathies and electrolyte disturbance, prematurity-related feeding intolerance, recurrent vomiting, and so on, which tend to respond to careful nutrition management. Growth during mid-childhood is highly dependent on the somatotrophic hormone axis and is less impacted by caloric manipulations. Growth in this period is usually lower than, but parallel to, percentiles of normal growth. Peripubertal growth is dependent on gonadotropic hormones. Puberty onset is often delayed by about 2 years. The pubertal growth spurt is limited by a reduced height velocity and duration [11], and this period of accelerated growth is often a time of more rapid renal function decline. Possible mechanisms include an increased glomerular filtration demand pitted against residual nephron mass and changes in hormonal physiology. The early (pre-dialysis) administration of recombinant human

growth hormone (GH) will improve height velocity, allow for catch-up growth, and increase final adult height [12]. While renal transplant corrects the metabolic and endocrine derangements associated with CKD, it does not fully correct growth disturbance, and post-transplant catch-up growth is usually limited.

Metabolic Acidosis and Renal Osteodystrophy

As CKD progresses to a GFR of about 50% of normal, metabolic acidosis results in decreased height and increased protein catabolism and should be treated aggressively with sodium bicarbonate or sodium citrate. It results from a number of renal abnormalities: reabsorption of filtered bicarbonate, reduced ammonia synthesis, decreased excretion of titratable acid, and decreased acidification of tubular fluid. Chronic acidosis results in changes in the ionic composition, resorption and deposition of bone, and blunts the trophic effects of GH. It reduces the renal generation of $1,25(\text{OH})_2\text{D}_3$ which, in combination with retained phosphate and hypocalcemia will eventually result in secondary hyperparathyroidism (sHPT) [13]. The low- and high-turnover skeletal lesions that occur with sHPT, namely, growth plate architecture abnormalities, epiphyseal displacement, fractures, and so on are clinically termed renal osteodystrophy. Treatment of sHPT includes calcitriol therapy to reduce PTH levels, or calcimimetics to suppress PTH secretion although long-term studies in children are ongoing. Not only is growth severely impacted by these conditions, but abnormal levels of PTH, 25-hydroxyvitamin D, phosphate, and fibroblast growth factor-23 are associated with increased mortality and CV disease in CKD [14].

Cardiovascular Disease and Risk Factors

As described earlier, CV disease is the leading cause of death in pediatric CKD, with risk 1,000 times higher in the ESRD population compared to the age-matched non-CKD population. It is well known that comorbidities of diabetes, hypertension and obesity are important contributors to the progression of CKD. Recent work by the CKiD cohort study and others [15, 16] showed that children with CKD have a high prevalence of CV risk factors, which remain even after the renal transplant. Forty four percent have dyslipidemia, 21% have abnormal glucose metabolism, and 15% have a BMI >95 th percentile [16]. Interestingly, 1 year post-transplant, the prevalence of obesity rises to 29% and 38% have metabolic syndrome [15]. Cumulative corticosteroid use and anti-proliferative agents have been speculated to be associated but no prospective study has analyzed this.

In the CKiD cohort, hypertension was present in 54%, and 17% had evidence of left ventricular hypertrophy. Systolic hypertension was associated with black race, glomerular etiology, shorter duration of CKD, obesity and elevated serum potassium [2]. What is of concern is that nearly half of the cohort had hypertension >90th percentile despite use of antihypertensive medication, which was less likely to be an ACE-I or ARB. Thirty eight percent of the CKiD cohort had masked hypertension, detected only on 24-hour ambulatory blood pressure monitoring (ABPM). Adult studies have shown that effective control of blood pressure (BP) reduces the rate of progression of CKD. The adult ESCAPE trial [17] used ramipril in all patients, plus alternate mechanism agents if necessary, to compare an intensified control approach reducing BP to <50th percentile vs. standard control to 50–90th percentile. The intensified control group had a slowed progression of renal disease with a 35% relative risk reduction. These studies suggest routine use of ABPM in all pediatric CKD patients to improve recognition of hypertension, and use of an ACE-I or ARB as part of an aggressive anti-hypertension management regimen.

Anemia

Anemia is linked to poor outcomes, poor QOL and neurocognitive ability in CKD patients [2]. Thus, a hemoglobin target of 11–12 g/dl and transferrin saturation >20% is recommended by KDOQI 2006 guidelines, targets extrapolated from adult studies. Forty five percent of children with CKD were found to be anemic in the CKiD cohort, with a more rapid decline as GFR fell below 43 ml/min/1.73 m² at a rate of –0.3 g/dl per 5 ml/min/1.73 m² [18, 19]. Multiple interrelated factors are contributing to anemia in CKD. Erythrocyte life span is shortened and is inversely proportional to blood urea nitrogen levels [18]. Intestinal blood loss is detected at a rate of 6 ml/m² BSA in non-dialytic CKD and increases in patients on hemodialysis (HD) [20]. HD patients lose blood to the dialysis equipment and tubing. There is alteration in erythrocyte and iron homeostasis physiology as well, and this is an important area of research and development and quality improvement in CKD.

Pediatric patients on dialysis require additional parenteral and enteral iron to maintain stores [11]. Hcpidin, a peptide produced by the liver, prevents absorption of iron into the circulation and is elevated in CKD and dialysis patients, which may explain the relative resistance to oral iron therapy. Both inflammation and iron loading promote hepcidin production, but erythropoietin (EPO) blocks its production by a mechanism not fully under-

stood. EPO production by the kidneys also declines with CKD progression. It does not induce erythrocyte proliferation; rather it suppresses erythroid cell apoptosis, which begins when the cells are deprived of EPO for a time as short as 2 h [11]. Administration of recombinant human erythropoietin (rHuEpo) IV 3 times weekly helps patients avoid red blood cell transfusions. In the pre-rHuEpo era, transfusions were required once per 3.3 treatment months in pediatric PD patients [21]. Darbe-poetin alfa, an EPO analogue, has a longer half-life and can be given every 2 weeks in pediatric patients with equal efficacy to the more frequent rHuEpo [22]. Newer synthetic analogues are being tested in Europe in the adult CKD population with mixed results.

Neurocognitive Impact and Quality of Life

Adults with childhood-onset kidney disease have limitations in the emotional, social and functional domains of life. CKD, even in mild stages [23], has an impact on neurocognitive ability, health-related quality of life (HRQOL), and anxiety and depressive symptoms [24]. These issues cannot be ignored during the most important stages of development. The most noticeable manifestation of CKD is short stature, associated with low scores in the physical, social, and overall HRQOL domains [23], but treatment with GH and catch-up growth is associated with improved HRQOL [25]. Anemia is associated with lower social domain scores [26], but it is unknown whether this improves with treatment. Lower measured GFR was associated with weakness, low energy, and daytime sleepiness, which in turn were associated with lower HRQOL [27]. Maternal education ≥16 years and a longer percentage of life spent with CKD were associated with higher overall QOL scores indicating an adaptation.

One of the CKiD initiative goals was to assess neurocognition across the spectrum of CKD. In the cohort, children with mild-to-moderate CKD fell within normative ranges for IQ, academic achievement and executive functioning, but were at risk for dysfunction with a significant portion at least one SD below the mean [28]. Importantly, they found no association between neurocognitive deficits and glomerular etiology, percentage of life spent with CKD, or hypertension. Higher GFR predicted improved academic achievement [28]. Unfortunately, the influence of race and socioeconomic status could not be studied in the CKiD cohort due to low representation. Longitudinal studies need to be performed to assess whether treatment of CKD morbidities or school intervention programs can alter QOL for these children.

Factors Affecting Progression of CKD

In a retrospective cohort study of patients with CKD stages 2–4 [29], children with glomerular disease were found to progress more quickly to ESRD than children with CAKUT anomalies. The authors generated a predictive model identifying severe proteinuria, glomerular disease, older age, non-Caucasian ethnicity, and patients who presented at stage 4 CKD, as leading to quicker progression. Risk categories formed from the preceding factors resulted in a probability of renal survival of 135 months for patients in the low-risk, 80 months for medium-risk, and 16.3 months for patients in the high-risk group. Multiple analyses from the CKiD cohort also support these findings. Wong et al. [30] showed that a 10% decline in eGFR was inversely proportional to a 14% increase in the urine protein-creatinine ratio, independent of the cause of CKD, and that non-Caucasian race was associated with higher levels of proteinuria. Both Wong et al. [30] and Warady et al. [31] found glomerular etiology was associated with a significantly more rapid decline. In the non-glomerular disease group, factors that led to faster decline were urinary protein-creatinine ratio >2 mg/mg, hypoalbuminemia, elevated BP, dyslipidemia, male gender, and anemia.

As described earlier, puberty is also associated with deterioration in kidney function. Data from the Italkid Project [32] showed that the probability of RRT was 9.4% during the first decade of life and 51.8% during the second decade. There was a clear break point at puberty in the kidney survival curve, with an ensuing decline after puberty in both males and females.

Transition to ESRD Therapies

Transplantation

Preemptive kidney transplantation is the therapy of choice in pediatric ESRD, and UNOS supports preferential allocation of young adult deceased donors to pediatric patients. Twenty eight percent of pediatric recipients from 1995 to 2000 were preemptive and this group has the best 1-year allograft survival. Twenty eight percent of transplants followed HD, and 34% followed PD [33]. Butani et al. [33] showed that longer duration of pre-transplant HD, but not PD, led to a linear increase in risk of allograft failure among living donor recipients. Transplantation conveys a 4-fold higher survival benefit compared to dialysis. However, there is a racial disparity in both access to preemptive kidney transplant [34] and survival of allograft. For reasons yet unknown, black recipi-

ents, regardless of high/low poverty neighborhood or public/private insurance, experience a much higher rate of graft loss 5 years post-transplant compared to other races [35]. As far as technical aspects of transplantation are concerned, size and age matching is generally not required. There are limitations to recipient size of 6.5–10 kg of body weight, which requires an intraperitoneal placement of the kidney with risk of migration in the abdominal cavity or compression of the allograft. New evidence-based immunosuppression regimens have led to a greatly improved acute rejection rate from 55% in the late 1980s to 10–15% most recently [36], and are extensively reviewed by Halloran [37].

Initiation of HD and Peritoneal Dialysis

Despite the multiple benefits of preemptive transplantation, there are situations where either HD or PD is necessary as a bridge. According to NAPRTCS data, the use of PD has declined over the last 30 years and in 2010, the use of HD surpassed the use of PD for the first time [4]. Recently, there has been attention in the literature on frequent HD or long-duration HD, both home and in-center, as a means to improve clearance and outcomes [38, 39]. Although distance from home to hospital dialysis center has previously precluded the use of HD, the option of home HD and telemedicine may change dialysis demographics in the near future. Despite all modalities of dialysis, the choice is influenced greatly by family participation and the geographic location of the dialysis center.

The decision to initiate dialysis in children is multifaceted, depending on residual renal function, laboratory values, psychosocial factors, and optimal timing of transplant. Estimation of kidney function is key in deciding when to initiate dialysis, but the readily available method using the modified Schwartz equation is less accurate at the lower range of GFR and with malnutrition. Measurement of serum protein cystatin C is a new alternative to estimate GFR, and can be used in the lower GFR range more accurately [40]. The KDOQI guidelines recommend considering dialysis at an eGFR <15 ml/min/1.73 m², while European guidelines recommend a threshold of 6 ml/min/1.73 m². Absolute indicators to begin dialysis include anuria, severe electrolyte disturbance, neurologic consequences of renal failure (e.g. encephalopathy, seizures, foot drop), pericarditis, bleeding diathesis, refractory nausea or hypertension, and so on. [11]. Malnutrition, or the inability to deliver full nutrition, is also a strong indicator to begin dialysis. The side effects of uremia, namely, fatigue and weakness, cognitive dysfunction, sleep disturbance, and gastrointestinal symptoms,

are considered relative indicators for dialysis. While there is a worldwide trend toward earlier initiation of dialysis to maximize nutrition, a majority of studies evaluating whether this method is beneficial have been performed in adults and are complicated by lead-time and selection bias. However, when considering early initiation, one must consider the effects of accelerated loss of renal function resulting from dialysis, psychosocial and school attendance impact, and the exposure to dialysis complications such as infection.

Unique Problems in Pediatrics

Bladder Dysfunction and Transplantation

The pediatric ESRD population, by nature of their most common underlying etiology of congenital anomalies, face unique problems in preparation for transplant. Posterior urethral valves, renal dysplasia, and so on lead to polyuria and bladder dysfunction not typically seen in adults. High pressure and low-compliance bladders during childhood with these lower urinary tract dysfunction conditions often lead to myogenic failure. Bladder augmentation is a strategy used to convert a high-pressure, low-compliance bladder into one of low pressure and improved compliance. Aside from the complications of augmentation cystoplasty itself, namely, lithiasis and risk for carcinogenesis in the intestinal segment, performing renal transplant into an augmented bladder has multiple feared complications, which could contribute to graft loss. These complications include reflux into the graft, UTI, bladder dysfunction, ureteral obstruction, mucus production from the intestinal segment causing outlet or foley catheter obstruction, especially in the immediate postoperative transplant period, and fistulae formation [41]. Post-transplant UTI is a significant complication in augmented bladders; however, possible contributing factors include inadequate clean intermittent catheterization (CIC) protocols, noncompliance with CIC, and inadequate consideration of polyuria or mucus production after transplant.

A systematic pre-transplant evaluation should be done in any child with CAKUT-related ESRD to include voiding cystourethrogram, urodynamic studies and imaging, evaluation of postvoid residuals and urinary leakage. Patients with bladder dysfunction should be evaluated again on a CIC regimen with anticholinergic medications as needed, and those that fail these conservative measures should be evaluated for augmentation cystoplasty, vesicostomy, or ileal diversion [42]. Jesus et al. [41] argues that augmentation can be performed with minimal risk

after transplant, as bladder compliance may change in the 6 months following transplant. There is lack of uniformity in the literature allowing for a comparison in outcomes between the various surgical strategies and timing in relation to transplant. However, the main concern with transplanting into a dysfunctional bladder without augmentation is the possibility of inducing the same damage in the grafted kidney as that which occurred in the native kidneys. For this reason, many support the argument for augmentation before transplant [42].

Adolescent Adherence to Medication and Transition to Adult Services

Adolescents have the highest rates of nonadherence to medication in pediatric transplant recipients [43], with increases in graft failure rates beginning at age 11 and peaking between ages 17 and 24 [44]. It is a complex developmental time, marked by a physical development that precedes emotional maturity, often with deficits in incite and judgement, organizational skills, risk perception, and logical reasoning, which evolve over time [45]. There may also be inadequate parental supervision or ineffective parent-patient or physician-patient communication, and depression/anxiety [43, 44]. All these contribute to risk factors for nonadherence whether intentional or not. Interventional strategies to improve compliance are generally effective if they involve a combined approach of health education, parental involvement, self-monitoring, reinforcement and problem-solving [43].

The transition from pediatric to adult care services is also a difficult and complex period. Patients with a functioning graft at age 17 have a 42.4% likelihood of losing the graft by age 24 [46]. Various studies have shown that transition to adult care at an age younger than 21 was associated with higher failure rates [47]. Medication adherence is assumed to be a major factor in graft loss during transitions. However, a recent study by Akchurin et al. [47] evaluated the differences of adherence in a transitioned vs. non-transitioned adolescent group and overall found no significant difference. Improved outcomes when transitioned at an older age may be related to survival bias, with those who successfully navigate adolescence being able to transition more successfully. Perhaps a more appropriate manner of transitioning young adults is in looking at overall cognitive and emotional cues for readiness rather than absolute age in years. Bell and Sawyer [45] recommend that patients should reach a series of critical milestones before transferring to adult care, which includes an ability to describe the etiology of their disease and need for transplant, and demonstration of a sense of

responsibility for their own health care. Once a transition has occurred, it is crucial for the pediatric and adult care providers to maintain contact, that adult providers are cognizant of unique complications specific to CAKUT anomalies and the ongoing developmental changes in the young adult population.

Conclusion

Pediatric CKD is a dynamic and complex medical and psychosocial disease with unique factors that separate this population from adults. The pediatric nephrology research community has made laudable and exciting efforts in focusing on this group, and evidence-based management of this population is growing. However, much is left

to be done on the topics of optimizing pre-transplant management of CKD progression and complications of growth and CV disease, optimizing dialysis and access, and improving post-transplant outcomes, especially in understanding why racial but not socioeconomic disparities exist in allograft survival. In order to further these research goals, multi-center cooperation and collaboration will be key, similar to what already exists and what is modeled by the Midwest Pediatric Nephrology Consortium, the CKiD cohort, and NAPRTCS.

Disclosure Statement

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