Pediatric Kidney Disease: Tracking Onset and Improving Clinical Outcomes

Carlton M. Bates, Jennifer R. Charlton, Maria E. Ferris, Friedhelm Hildebrandt, Deborah K. Hoshizaki, Bradley A. Warady, and Marva M. Moxey-Mims, on behalf of the Kidney Research National Dialogue

Abstract
Recent studies confirm that much of adult kidney disease may have its origins in childhood, often as a result of abnormal or suboptimal fetal kidney development. Understanding of the etiology and pathogenesis of CKD in children is rapidly evolving because of robust longitudinal clinical data, identification of monogenic mutations related to common causes of CKD, and improved knowledge of factors that influence the onset and progression of CKD. The Kidney Research National Dialogue, supported by the National Institute of Diabetes and Digestive and Kidney Diseases, asked the research and clinical communities to formulate and prioritize research objectives that would improve understanding of kidney function and diseases. This commentary outlines high-priority research objectives to assess factors associated with the predisposition to develop renal disease in children, and address the unique challenges in treating this population.


Introduction
The National Institute of Diabetes and Digestive and Kidney Diseases asked the community to identify research objectives that, if addressed, would improve our understanding of basic kidney function and aid in the prevention, treatment, or reversal of kidney disease. Through the Kidney Research National Dialogue (KRND), >1600 participants posted >300 research objectives covering all areas of kidney disease. This commentary focuses specifically on opportunities to advance the knowledge of factors related to the onset and progression of pediatric kidney diseases, as well as the diagnostic and treatment-related events that occur over a child’s life course (Figure 1).

In the first 2 decades of life, congenital anomalies of the kidneys and urinary tract (CAKUT), nephrotic syndrome, and renal cystic ciliopathies are responsible for 45%, 15%, and 5% of CKD cases, respectively, on the basis of data from the North American Pediatric Renal Trials and Collaborative Studies. Many factors influence the onset and progression of pediatric kidney diseases, as well as the diagnostic and treatment-related events that occur over a child’s life course (Figure 1). Genetic factors likely interact with the prenatal environment to cause developmental abnormalities, intrauterine growth restriction, and premature birth. Both the development of CAKUT and abridged renal development seen with prematurity compromise the final functional renal mass. Hence, low nephron number might predispose the child to later disease as a result of insufficient renal reserve. The rate of CKD progression is also affected by clinical exposure to AKI, hypertension, obesity, and diabetes mellitus. Studies such as the Chronic Kidney Disease in Children (CKiD) cohort study are providing valuable clinical data detailing risk factors for CKD progression and its associated complications. These findings will expand our understanding of disease mechanisms and improve genetic counseling, etiologic classification for clinical trials, and screening for potential therapeutic agents.

Below are the areas of investigation proposed through the KRND process.

Research Objectives
1. Find Genetic and Environmental Factors That Affect Prenatal Kidney Development
Animal studies have revealed many genetic and some environmental causes of CAKUT. Despite recent studies that validate the role of these insults in human cases of kidney and/or urinary tract maldevelopment (1), as well as the recent successes in the identification of causal genes of CAKUT via high-throughput sequencing, the majority of the causes of human CAKUT remain unclear. The emerging number of repositories with biosamples from pediatric populations offers the possibility of finding novel causes of CAKUT. In addition, advances in our knowledge of the underlying mechanisms regulating the establishment, maintenance, and differentiation of murine renal progenitor cells has led to paradigms for manipulating nephron number and determinants of kidney endowment.

Patient-oriented, translational studies have established associations of low birth weight and premature birth with reduced nephron number and predisposition toward renal disease. Robust studies of the antenatal and perinatal environments and their relationship to important long-term outcomes are needed. The fetal response to extreme maternal undernutrition can be traced in
studies based on the Dutch famine and have revealed the persistence of epigenetic markers of key genes involved in growth and development. Thus, advances in understanding the fetal response to undernutrition in model organisms that focus on nephron number, perhaps in concordance with clinical studies (e.g., CKiD), would increase knowledge pertaining to the control of nephron endowment and functional renal mass. It is thought that nephron number is determined at the time of birth with no known capacity for nephron regeneration. Testing whether low nephron number contributes to the development of kidney disease is stymied by the lack of noninvasive ways to quantify nephron number/function and fibrosis in humans. However, newer techniques, such as magnetic resonance imaging detection of charged ferritin binding to glomerular basement membrane or diffusion tensor imaging, might allow repeated assessments to provide insight into the development of progressive kidney disease or measurement of nephron regeneration, and might aid the design of therapies to halt CKD advancement. These efforts will require close collaboration between pediatric nephrologists, maternal-fetal medicine specialists, neonatologists, and developmental biologists.

2. Identify Genetic Causes of Pediatric CKD

The number of known causative genes contributing to the pathogenesis of pediatric CKD in children is growing, and additional investigative efforts are likely to reveal an increased fraction of cases with an identifiable monogenic cause of CKD. These findings will have major implications for the diagnosis and treatment of early-onset CKD. Not only will detection of the causative mutations provide an unequivocal diagnosis, but this may prove to be an important determinant of outcome. In addition, the determination of causative genes will inform our understanding of pathogenesis and enable the generation of gene-specific animal models to conduct high-throughput drug screening.

3. Understand AKI in Neonates

The potential to reduce the morbidity, mortality, and cost of care for neonates depends on our ability not only to accurately diagnose AKI, but also to define patient characteristics, improve our general epidemiologic and ecologic understanding of risk factors, and determine the optimal time and methods for intervention. Over the last several years, accumulating evidence supports the connection between AKI and CKD in both the adult and pediatric populations (2,3). Whereas standard definitions of adult AKI are improving, the definition of neonatal AKI, particularly for the premature neonate, is confounded by both the natural changes in newborn GFR and the ability to secrete creatinine in an immature tubule. Unlike in adults, the long-term effects of neonatal AKI have not been rigorously studied. There is potentially a larger mismatch of nephron reserve and lifespan in the infant who has suffered AKI compared with an adult who has suffered AKI. While neonatal AKI can be stratified in many ways (due to asphyxia, nephrotoxins, nephron immaturity, or congenital cardiac disease), it is important to understand the biologic or physiologic influences in each subpopulation so that therapies, interventions, and ongoing follow-up are appropriately focused. Multicenter collaborative efforts between pediatric nephrology and neonatology will be required, given the relatively small numbers of affected neonates at individual sites.

4. Develop Predictive Tools and Specific Treatments for Pediatric Kidney Disease

As genetic mutations and predispositions are known, it may be possible to specifically target different pathways in

![Figure 1. Life course of pediatric-onset CKD. This timeline shows progression of pediatric-onset kidney disease from aberrant prenatal development, through insults to the kidney during childhood and on into adulthood. The effect of both clinical and lifestyle exposures is shown. The lower panel shows the high-priority research objectives needed to improve outcomes at different points in the life course. CAKUT, congenital anomalies of the kidneys and urinary tract.](image-url)
children, rather than extrapolate from adult studies. There is a need for predictive tools to assess the likelihood of predisposition for renal disease. Recent studies have revealed a wealth of biologic molecules and cells within the urine that could be harnessed as predictive tools. Systematic analysis to determine the transcriptome, proteome, and metabolome of urine from prospective trials or studies, such as CKID or the Randomized Intervention for Vesicoureteral Reflux, might provide such tools.

In addition, drugs are metabolized differently in infants and children; thus, studies are needed to determine how to tailor medication use in pediatric populations with CKD. Pharmacokinetic studies as well as clinical studies that incorporate pharmacogenomic and pharmacometabolomic data should help to “personalize” therapies with a goal of increasing drug efficacy and minimizing toxicity.

5. Improve Treatment Adherence

The effect of nonadherence on healthcare costs and morbidity is substantial. Adolescents are known to exhibit a high degree of nonadherence, putting them at risk for accelerated disease progression, in addition to renal allograft loss in the transplant population. Although biomarkers of adherence are available for people who receive immune-modulators, the definition of nonadherence has not been agreed upon by CKD/ESRD researchers. Further study is needed to better understand risk factors for nonadherence, especially those that are potentially modifiable. On the basis of current knowledge of this long-standing clinical challenge, and with the ubiquitous use of electronics and social media for communication in this age group, the development of a multifaceted platform of interventions aiming to improve adherence is warranted. This could incorporate peer interactions in addition to any “outside” efforts from medical caregivers and parents. Studies could be structured to test whether the implementation and utilization of social media platforms, specifically tailored to the needs of the individual, might improve adherence and health outcomes in the adolescent population.

6. Enhance Self-Management and Healthcare Transition from Child to Adult

To improve the health outcomes of adolescents and emerging adults with CKD/ESRD as they transfer to adult-focused health services, self-management and healthcare transition preparation is critical and cost-effective (4). This preparation from parent-directed care to disease self-management should be planned and monitored longitudinally, with the participation of the youth, caregiver, and interdisciplinary health providers from both child- and adult-focused practices (5). A life course approach needs to be developed and embraced in both pediatric and adult practices, implementing patient/caregiver education programs that are culturally and literacy-level appropriate. Innovative approaches are needed to characterize specific population and sex-based challenges to effective transitioning of adolescents to adult care. Most importantly, the definition of successful healthcare transition outcomes, tools to diagnose and measure healthcare transition preparation and implementation, and models to guide interventions need to be developed and validated.

Although understanding health outcomes for children is important, new initiatives designed to train pediatric and adult nephrology providers (along with primary care and family medicine providers) how to care for those with congenital and childhood-acquired kidney disease are vital. Evidence-based curricula on developmentally appropriate care for survivors of pediatric-onset CKD/ESRD will need to pay particular attention to disease etiology, percentage of life with the disease, and medical/psychologic comorbidities.

Conclusion

Although our understanding of pediatric-onset kidney disease is improving, some key steps are needed to make strides in therapy and self-management. These include a better understanding of the underlying genetic and maternal environmental effects contributing to a predisposition toward CKD and an appreciation that the neonatal/pediatric kidney is not the same as an adult kidney and, thus, better disease definitions for the pediatric patient are required. The latter should lead to the development of pediatric-specific therapies, including targeted medications. In addition, this population would benefit from strategies to improve treatment adherence and training of the medical workforce in a life course approach to care.

Acknowledgments

The Kidney Research National Dialogue was developed and implemented by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Division of Kidney, Urologic, and Hematologic Diseases staff and directed by Dr. Krystyna Rys-Sikora. The Pediatric topic was facilitated by Drs. M.M.M.-M. and D.K.H. The complete listing of areas of research emphasis, in priority order, is available on the NIDDK KRND webpage (http://www.niddk.nih.gov/about-niddk/offices-divisions/division-kidney-urologic-hematologic-diseases/kidney-research-national-dialogue/Pages/kidney-research-national-dialogue.aspx). Please visit this website for updates on KRND.

Disclosures

None.

References


Published online ahead of print. Publication date available at www.cjasn.org.

This article contains supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.00860114/-/DC1Supplemental.