Improving CKD Therapies and Care: A National Dialogue

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Abstract
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 our understanding of kidney function and diseases. This commentary outlines the high-priority research objectives for CKD. The goal of these research objectives is to enhance knowledge to improve outcomes in people with CKD. Basic and translational research, longitudinal observations, and epidemiologic studies can each point to targets for intervention. Future interventions must be informed by data from well designed, large representative observational studies that include collection of genetic and phenotypic data as well as biospecimens. Interaction of genetic and environmental factors must be part of the analysis, including the influence of diet, comorbid conditions, and medication. The focus should be not only on slowing or preventing progression of CKD, but also on regression of disease to the greatest extent possible.


Introduction
The kidney is critically involved in control of blood pressure, the synthesis of erythropoietin and vitamin D, glucose homeostasis, regulation of the renin-angiotensin-aldosterone system (RAAS) and maintaining electrolyte and acid-base balance. CKD can result from a multitude of acquired or inherited diseases. Most people with CKD in the United States are aged >60 years but the youngest individuals may be at the greatest risk for sustaining developmental and social dysfunction in a disease characterized by life-long progression (1). A common issue regarding CKD is its tendency to progress, and new interventions are needed to reverse or ameliorate this process (1).

The Kidney Research National Dialogue (KRND) recruited members from the renal community, including basic and clinical scientists, practitioners, and advocacy and professional groups, to provide the National Institute of Diabetes and Digestive and Kidney Diseases with advice regarding strategic opportunities and emerging innovations in the field of CKD. A key theme of this commentary is the importance of bringing together the spheres of basic and translational research, epidemiology, clinical observations, and ongoing clinical trials to enhance knowledge about CKD and improve outcomes for people with CKD (Figure 1).

The research objectives identified through the KRND can be divided into seven categories, aimed at enhancing prevention, prognosis, treatment and outcomes, thereby improving clinical care and quality and length of life for people with CKD.

Research Objectives
1. Understand Genetic and Environmental Factors Involved in Initiation, Progression, and Outcomes of CKD, with Emphasis on Longitudinal Observation of Population-Specific Risk
   - Characterize the interactions between nephropathy susceptibility genes and modifiable environmental exposures likely to play critical roles in the initiation and progression of CKD.
   - Implement birth cohort studies to identify causative environmental and genetic factors involved in later CKD, leveraging careful phenotyping and long-term longitudinal follow-up. Study factors including low birth weight, prenatal exposure to inadequate maternal nutrition, placental insufficiency, or exogenous hormones (e.g., glucocorticoids), medications, or toxins, and history of AKI during the neonatal period.
   - Identify effects and mechanisms of early exposures including the potential role of epigenetic modifications secondary to viruses on the lifetime risk of adult diabetes, hypertension, obesity, and kidney and cardiovascular disease.
   - Examine the effect of ethnic disparities and genetic variation (including known genome-wide association studies [GWAS] or GWAS hits) among population groups on the development and progression of CKD.
   - Characterize interactions between gene variants and hypertension, biomarkers (e.g., fibroblast growth factor-23), epigenetic modifications and modifiable environmental exposures, and apol1 (APOL1) gene variants in various informative populations. Interrogate how genes that promote salt sensitivity and hypertension may exacerbate CKD progression.
Develop clinical trials evaluating outcomes in CKD among multiple population groups integrating genomic and pharmacogenomic approaches to identify individuals and populations with specific risk factors who may benefit the most from intervention.

2. Evaluate the Role of Obesity and Diet in CKD
- Examine how diets high in animal protein, animal fat, saturated fat, sugar, or sweetened soda, and Western dietary patterns are associated with albuminuria and greater decrease in eGFR in observational studies.
- Evaluate the effect of high dietary vegetable and fiber sources on dietary phosphorus load and production of toxins, such as p-cresol and indoxyl sulfate, in CKD progression.
- Examine the role of obesity, higher body mass index, and central adiposity as independent risk factors for CKD.
- Develop interventional trials to assess the association of diet with atherosclerosis and endothelial dysfunction in people with CKD.

3. Navigate the Psychosocial Milieu of CKD in Adolescents and Adults
- Expand awareness of the unique obstacles to achieving normal development for youth with CKD cared for by adult-focused physicians.
- Develop innovative preventive approaches to non-adherence and risk-taking behaviors in order to lessen negative outcomes among youth and adults with CKD.
- Determine best practices in preparation for transition from pediatric care to adult-focused providers for youth with CKD, including delineating developmental markers useful for longitudinal assessments.
- Promote the National Kidney Disease Education Program and enhance its effect on CKD awareness, prevention, and treatment.

4. Promote Translational and Clinical Research in Specific Areas of Hypertension
- Assess the roles of sex steroids and sex in hypertension and renal disease. Sex-specific therapies may be required to achieve clinical goals and should be evaluated.
- Continue to investigate pediatric hypertension, including the natural history, risk factors, and prevention of cardiovascular disease. Couple GWAS in populations at risk, such as African Americans, Latino Americans, and obese children and those with sustained high BP, with phenotypic data, and compare these studies to normal populations during growth and development.
- Investigate the causes of labile hypertension, salt sensitivity, development of cardiovascular disease, and sleep disorders in people with CKD.

5. Study Alkali Therapy to Slow the Progression of CKD
- Alkali therapy has been shown in small studies to be effective in slowing the progression of CKD, even at stages in which blood chemistries do not reflect acidosis. Because
alkali therapy is safe and inexpensive, it could prove to be a valuable addition to RAAS blockade.

- Develop a comprehensive clinical trial of alkali-based therapies to prevent and attenuate the progression of CKD.
- Assess the use of dietary fruits and vegetables to reduce net acid production and prevent hyperkalemia in people with CKD.
- Evaluate these responses in CKD attributable to hypertensive kidney disease, CKD without specific diagnoses, polycystic kidney disease, and diabetic nephropathy.

6. Explore New Therapeutic Directions

- Characterize the best therapeutic approach and timing of intervention for interruption of the RAAS to prevent and slow the loss of function in people with CKD.
- Identify new and potentially more potent antagonists of progression, such as antifibrotic agents and uric acid-lowering drugs, and test them in clinical trials in people with CKD.
- Determine whether lowering uric acid levels, perhaps in combination with other interventions, such as alkali therapy and dietary modifications, plays a role in changing the course of CKD.
- On the basis of findings in longitudinal cohorts, develop sex-specific therapeutics for hypertension and CKD progression.

7. Advance the Care of People with Cardiorenal Syndrome

- Identify the mechanisms by which congestive heart failure develops in advanced CKD, and how the development of congestive heart failure in people without kidney disease is accompanied by a concomitant, marked, and sometimes irreversible decrease in GFR.
- Establish evidence-based treatments for the cardiorenal syndrome in order to lessen its association with increased morbidity and mortality.

The overall goals of the above-listed objectives are to enhance knowledge and improve outcomes in people with CKD (Figure 1). Undertaking basic and translational research, longitudinal observations, and epidemiologic studies may pinpoint novel targets for intervention. At this time, there are many knowledge gaps regarding sex differences and genetic influences within the pediatric population. Future interventions must be informed by data from well designed, large representative observational studies that include collection of genetic and phenotypic information as well as biospecimens.

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