National Institutes of Health
National Institute of Diabetes and Digestive and Kidney Diseases
Gut Microbiota and Kidney Disease

Virtual Meeting

May 28–29, 2024

EXECUTIVE SUMMARY

The National Institutes of Health (NIH) sponsored a scientific workshop on May 28 and 29, 2024, titled "Gut Microbiota and Kidney Disease," that was hosted by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). This workshop addressed the overall impact of the microbiome and microbiota on kidney diseases, with specific focus on their role as markers, mediators, and amplifiers of kidney function and dysfunction. In addition, the workshop explored the biological and mechanistic interplay between the kidney and the gut microbiome. The workshop also discussed a roadmap for future studies, which will help define novel associations between gut microbiota and kidney diseases, identify mechanisms linking gut microbiota and kidney diseases, and assess the clinical value of gut microbiota in diagnosing and treating kidney diseases.

The objectives of the workshop were to—

- Advance the understanding of the gut microbiota and kidney disease nexus, which could lead to answering the central question of whether changes in the gut microbiota or microbiome can be an early measure of kidney dysfunction.
- Bring together relevant disciplines to address the state of the science, identify gaps in knowledge relevant to establishing the diagnostic role of gut microbiota in kidney diseases, and encourage collaborative efforts in the field.
- Discuss best approaches to study microbiota in kidney diseases across the spectrum of kidney diseases to be studied.

The workshop began with opening remarks from Dr. Robert Star, Director, Division of Kidney, Urologic, and Hematologic Diseases (KUH), NIDDK, and Dr. Deepak Nihalani, Program Director, KUH, NIDDK, followed by a patient talk focused on the importance of research in this field. Next, leading experts presented their research across four scientific sessions. These sessions encompassed microbial dysbiosis as a cause or consequence of kidney disease, gut microbiome–drug interactions, the prognostic value of gut microbiota and metabolites in kidney disease, and gut microbiota as a novel gateway to kidney disease therapeutics. During their presentations, the speakers highlighted the next level of challenges and opportunities in the field, as well as approaches for moving the field forward in an innovative way. The attendees also participated in breakout sessions that corresponded with the four topics of the main sessions to discuss approaches and challenges in each area.

Background

Microbes are the most abundant resource on Earth, yet their value in human disease is not fully understood. The gut microbiome is a dynamic ecosystem that reflects the body's response to various systemic pathologies, including kidney diseases. The scientific community has contributed numerous landmark publications on microbes, but knowledge remains limited on the direct interaction between the gut microbiota and human health, particularly in the context of kidney diseases. Novel approaches, particularly in patient-centered research, will help elucidate the dynamics of the gut microbiota and kidney disease.

Session 1: Microbial Dysbiosis—A Cause or Consequence of Kidney Disease

In the first session, speakers discussed approaches to deciphering the gut microbiota–kidney disease nexus, developing and refining tools and models for investigating the gut microbiota and kidney diseases, and understanding the role of disease-causing metabolic pathways that are influenced by the microbiome. Presentation topics included the gut microbiome in chronic kidney disease (CKD); dietary metabolism, the gut microbiome, and cardio-renal diseases; challenges and prospects for microbiome-based interventions; high-throughput discovery of microbial biochemical mechanisms; intestinal microbiota, CKD, and cardiovascular disease; metabolite-based host–microbe interactions in the intestinal tract; and metabolic and migratory links between the gut microbiota and kidney disease.

Research Gaps and Opportunities

- More work is needed to disentangle the dynamics of cause and effect regarding gut microbiome dysbiosis and disease. Clear definitions of gut microbiome dysbiosis, as well as the healthy microbiome, are necessary for comparative studies. Microbiomes—during both health and dysbiosis—vary among individuals. Therefore, it is challenging to identify consistent patterns for clinical practice. Longitudinal studies can provide insights. Additionally, more work is needed to identify biomarkers that can be translated for clinical use. It is crucial to understand not only associations, but mechanisms of specific microbiota and disease.

- Next-generation sequencing approaches provide opportunities for comparative microbiome studies. Every human has a unique collection of microbes, and the lack of consistency in microbial populations makes microbiota data sets very complex; thus, studies on this topic often remain underpowered and irreproducible. Sampling methods also can influence results. No single tool exists that ideally works for all sample types; therefore, standardized methods are needed that can be optimized and verified to address the challenges of interindividual variations in microbial populations. Researchers can overcome these challenges by employing complementary approaches involving novel sequencing techniques and mechanistic and culture studies; however, these methods will require appropriate validation.

- Multiple gut microbiota interventions exist, including fecal transplants, diet and probiotics, antibiotics, and small-molecule inhibitors. Altering the microbiota is fundamentally an ecological problem, however, and any intervention will incur complex off-target effects. Identical interventions can lead to different results among individuals, depending on the baseline microbiota; a better understanding of these interventions is needed. Microbiome data can provide insights into therapeutic strategies. Proof-of-concept clinical trials also can be valuable in assessing the therapeutic value of gut microbiota.

- Computational methods can provide insight into understanding taxonomic, functional, and genetic profiles of microbial communities. Progress in this area can enable meta-analysis and identification of different microbial strains that may be present in microbial communities. With this approach, researchers can identify priority gene and protein families for targeting. More population-level multiomics studies are needed to obtain further insight in this area. A molecular understanding of the microbiome is critical. Research on microbial associations and communities, rather than individual species, can provide insight for novel intervention strategies. Tools for this work are available, and case studies will be valuable for modulating the gut microbiota for therapeutic purposes.

- The burden of CKD is increasing globally, and multimorbidity is becoming more prevalent. CKD-associated microbiome changes are complex; more work is needed to identify the causes of CKD-associated microbiome features. The stage and cause of CKD must be considered in

developing therapeutics. Additionally, nutritional counseling—guided by biomarkers—can help control metabolic effects.

Breakout Discussion

- Gaps exist in the understanding of the relationship between gut microbiota and kidney disease. Major themes include lack of information on host–microbe interactions, receptors, activated pathways, influence on host immune function, and effects on the kidney. More research is needed to understand the mechanisms of kidney disease (e.g., models, disease types, disease stage and progression). Data (e.g., longitudinal) are also needed to better understand these topics, and metadata will be crucial.

- The contributions of host metabolic pathways in microbiome-related disease are not fully understood. Studies of energy metabolism and resource competition can help researchers identify common pathways that are involved in kidney disease. Cardiovascular disease is both a consequence and cause of renal dysfunction, and these dynamics are challenging to understand. A more complete understanding of cardiovascular disease will be essential.

- Microbial disturbances might not be a single cause of disease, but manipulation of community dynamics could affect disease progression. Lack of consensus on microbial dysbiosis and disease remains a challenge in this area. Researchers should be intentional in the language that they use to describe changes in microbial communities (e.g., disease-associated metabolic pathway perturbations). Factors for consideration include host susceptibility, environment, and social determinants of health; these must be evaluated alongside the microbiome to understand the full picture.

- All models have limitations, and multiple types of studies (e.g., large-scale human studies, animal models, *in vitro* and *in silico* models) are necessary to study this topic from different angles. Small interventional studies, with collected samples and metadata, could be valuable for therapeutic development and large-scale data analyses. The lack of a germ-free rat model remains a gap within the field. Additionally, a mechanistic understanding of disease is essential for effective modeling.

Session 2: Gut Microbiome–Drug Interactions—A Two-way Street

In the second session, panelists spoke on their efforts to define the role of the gut microbiome in therapeutic metabolism and how drugs affect the gut microbiome; to determine how changes in the gut microbiota affect therapeutic efficacy, toxicity, and personalized medicine approaches; and to delineate how the gut microbiome specifically alters commonly used CKD therapeutics. Presentation topics included targeted inhibition of the gut microbial trimethylamine N-oxide pathway for the treatment of CKD, metabolic organ communication by sodium–glucose cotransporter 2 inhibition, small molecules from the human microbiota, a pharma[e]cological view of precision medicine, and gut microbial enzymes in kidney disease and transplantation.

Research Gaps and Opportunities

- Therapeutic drugs affect the microbiome, and changes in the microbiome influence their pharmacokinetic and pharmacodynamic properties. These dynamics represent a barrier to drug development and administration, and more work is needed to understand them. Drug interactions and shared metabolic pathways also must be considered in this context. Therapeutic drugs are a critical tool for both research and clinical treatment.

- Gut microbiota are an emerging therapeutic target for cardiometabolic diseases. The kidney serves as a hub for metabolism in humans, but more work is needed to understand the molecular tissue pathophysiology and identify new targets for CKD and cardiovascular disease. Deciphering organ metabolic communication will increase researchers' understanding of cardio-renal-metabolic pathophysiology.
- More work is needed to better understand how signals from the gut microbiome are sensed in the kidney, as well as to learn more about the systematic renal bioreactivity of microbial compounds. Additionally, a gap remains in researchers' understanding of transporters and secreting proteins within the kidney. Future efforts could focus on enhancing excretion of key gut metabolites.
- Defined complex microbial communities can be used to provide insights into molecular mechanisms of phenotypes. Researchers can use this approach to better understand the physiological and metabolic adjustments in response to changes among microbially derived metabolites. An understanding of the gut microbial enzyme dynamics, as well as the metabolome, can help researchers move toward personalized approaches to improve clinical outcomes in kidney transplantation.
- Genetic tools can be useful for testing mechanistic hypotheses regarding the microbiome and drug responses. Activity-based proteomics profiling can be a powerful tool for examining metabolite binding and activities. Metaproteomic and metatranscriptomic approaches also could be considered.

Breakout Discussion

- The interplay between the microbiome and drug metabolism is critically important to human health, and approaches for studying this topic (e.g., models, controlled dietary studies) are needed. New tools can be leveraged to define kidney diseases at a molecular level. Rare genetic conditions also can provide valuable insights into the roles of specific genes. Researchers are interested in defining kidney diseases at the molecular level and tailoring examinations accordingly.
- Challenges in this area include multimorbidities, interplay among organ systems, sex differences, and translatability of animal models. Researchers have provided ample evidence suggesting that drugs and the microbiome affect one another. The roadmaps for studying these dynamics exist in the literature, but more work is needed to understand the effects of specific drugs on the gut microbiota. Immunotherapy approaches are likely to affect the microbiome in ways that can be either informative or disruptive from a clinical perspective. Isotope labeling and community approaches will be valuable for understanding interactions between compounds and microbiota. Well-controlled studies can provide insights into mechanisms that are relevant to therapeutic drugs and metabolites.

Session 3: Prognostic Value of Gut Microbiota and Metabolites in Kidney Disease

In the third session, presenters discussed ways to evaluate the gut microbiota and fecal metabolites as noninvasive biomarkers for CKD and acute kidney injury (AKI) diagnosis. Presentation topics included the importance of gut microbiota and metabolites in predicting the circulating metabolome and CKD progression; identification of a commensal as a potential biomarker or therapy for kidney disease; progression of diagnostics in the microbiome field, from ecology to machine learning to artificial intelligence (AI); and therapeutic bubble tea for the removal of uremic toxin precursors from the gut.

Research Gaps and Opportunities

- Gut microbiome pathways can help explain variance in the fecal metabolome, and gut microbiota can help predict individual fecal metabolite levels. Many of these metabolites are associated with kidney function and can be explained by pathways related to immune and inflammatory responses, amino acid handling, lipid metabolism, and carbohydrate metabolism.
- Studies are needed to explore potential pathways for these associations (e.g., compositional dysbiosis, disruption of gut barrier function, reduced renal clearance of gut-derived metabolites). Future work could focus on mechanisms through which gut-derived metabolites could promote CKD morbidity. More human studies with stool samples and longitudinal follow-up are also needed. In the future, it would be helpful for researchers to consider absolute quantification rather than relative abundance. The methods for such studies require specific expertise.
- Microbiome science is now limited primarily by the ability to analyze, rather than generate, data. AI helps researchers improve predictions and provides new capabilities (e.g., transfer learning, upscaling, large language models). Future developments include connection of functional pathways and phenotypes in CKD, group- and individual-level predictions of intervention outcomes, and natural language interaction with data sets.
- Basic and clinical research needs in this area include prospective longitudinal studies, intervention studies, more diverse cohorts, interfaces for analysis techniques to improve accessibility for the research community, and better taxonomic and functional gene identity. Microbiome-based medicine represents a new paradigm for the treatment of hypertension. Needs in this area include mechanistic studies, tools, and human resources.
- New approaches show promise for the removal of uremic toxin precursors from the gut, but off-target effects should be considered. Testing in animal models and clinical trials will provide further insight into this topic.

Breakout Discussion

- Researchers are moving beyond a simple understanding of taxa and are working toward studies focused on metabolites and function. Additionally, researchers can study activities, rather than expression only. More work is needed to understand changes over time, as well as individual variability.
- Quantitative assays are critical for metabolomic testing; this approach will allow researchers to characterize metabolite identities and levels, with a goal of understanding biological mechanisms. Good databases are key for consistency across studies, and AI tools could be considered for developing new pipelines.
- New biomarkers are needed, but study feasibility must be considered. The application of these biomarkers for prognosis and diagnosis, as well as detection of changes in disease, should be considered. In particular, biomarkers can be critical for new targets, and more consideration in this space is needed.

Session 4: Gut Microbiota—A Novel Gateway to Kidney Disease Therapeutics

In the final session, presenters spoke on approaches to explore microbe-versus-host targeted interventions and leverage advances in microbial engineering to create smart bacteria to benefit patients with kidney disease. They also strategized on how to use beneficial microbes and microbiome-based therapeutics to improve kidney function. Presentation topics included the gut microbiome and glomerular filtration rate (GFR); gut microbiome and AKI; gut microbiome and kidney stones; the ecology of the human small

intestinal microbiota; multidrug-resistant organism (MDRO) colonization and infection in renal transplant recipients with microbiota transplantation; prebiotic and microbial co-metabolism in CKD; targeting a microbial pathway for management of kidney disease; effects of diet on the gut microbial proteome and renal function, oxalobacter formigenes-derived peptides with therapeutic potential for hyperoxalemia, hyperoxaluria, and related kidney stones; and a gut microbial pathway to treat hyperuricemia in CKD.

Research Gaps and Opportunities

- Gut microbes regulate GFR in healthy mice, but knowledge gaps remain regarding the types of microbes, mechanisms of mediation in the host, involvement of metabolites, toxicity, dysregulation of signaling, and manipulation of the system to elevate GFR in disease. Additionally, more work is needed to understand how microbes regulate other aspects of health. Researchers also are interested in pursuing more direct interventions in this space.
- Amoxicillin induces specific changes to gut microbiota and offers a potential treatment for severe AKI. Prebiotics also could be considered in this context. Knowledge gaps remain regarding how the microbiome modulates the early injury phase of AKI and mediates recovery and repair from AKI, how microbes communicate with the kidney and which key microbes mediate AKI, how AKI modifies the gut microbiome, and approaches for designing clinical trials on this topic.
- Many bacteria degrade oxalate, and multilayered co-occurrence network analysis of operational taxonomic units revealed a significant correlation with consumption. Challenges in this area include oxalate consumption requirements, potential adverse effects, and poor patient selection. To date, few drugs have been developed to address oxalate. A genetic platform for rapid manipulation of functions would help advance research in this area. Additionally, a potential role for bacteriophages could be explored in the future.
- CKD is a major risk factor for hyperuricemia and gout, and drug contraindications make treatments for these patients challenging. Urate-degrading bacteria could offer therapeutic potential. Challenges in this space include engineering, location, tolerance, additives, and models. This approach could be translated to various mechanisms within the field.
- New approaches to understanding the small intestine microbiota offer important implications for modulating their effects. Future topics include changes in the small intestine microbiota during disease; effects of antibiotics, prebiotics, and diet on the small intestine environment; and approaches to precision-engineering the small intestine microbiota through spatial fecal microbiota transplants. More work is needed to understand the long-term effects of antibiotic treatment.
- Numerous approaches, varying in specificity and magnitude, have been developed to perturb the native microbiome. Prebiotics offer a potential strategy for helping to control gut microbiota. Furthermore, multiple factors (e.g., sex differences, diet, environment) influence gut microbiota, and more work is needed to understand the dynamics of these factors and develop preventive and therapeutic strategies.
- Intestinal microbial communities are well established as critical to MDRO resistance. Fecal microbiota transplantation may reduce antimicrobial resistance genes, MDRO colonization, recurrent infections, bloodstream infection, and all-cause mortality. Future work could include conducting human microbiota intervention trials to understand dynamics in relevant hosts, developing novel methods to track low abundance strains, and performing shotgun metagenomic sequencing to detect strain dynamics.

Breakout Discussion

- Basic scientific knowledge of the gut microbiota is critical to developing therapies for kidney disease. Certain microbes appear to be beneficial, but context must be considered; specific microbes are likely to be appropriate for certain indications. Therapeutic development is challenging, and success in preclinical studies does not always translate to success in clinical trials.
- Microbes function as a community, and future therapeutics could be designed from this perspective. Function, rather than simply taxa, can help inform agent selection. Deficiency and functionality of microbial communities must be considered across disease processes, particularly in the context of nutrition. Additionally, variation among patients can influence responses to drugs.
- To date, few appropriately vetted therapies have been developed in this space. Diet represents a promising existing strategy for modulating the gut microbiome. Compliance with diet-based treatments, however, remains a concern. Genetically engineered bacteria (e.g., loss of function) could represent a potential treatment strategy.

Summary

The Gut Microbiota and Kidney Disease Workshop featured discussions focused on future opportunities and directions for the field. Key themes that emerged during these discussions include a complete understanding of microbial dysbiosis, progress in multiomics research, development of new analytical tools for characterizing microbial metabolites and proteins, systemic inflammation as a contributing factor to CKD, the inherent diversity of the host and microbes, current unknowns in the field, the importance of multiple approaches in studies, promising microbial enzyme inhibitors, the function of metadata in designing future studies, and the need to understand how microbial compounds interact with hosts and host pathways. Overall, participants recognized that the gut microbiota demonstrate promise for the diagnosis and treatment of kidney disease; they agreed on the need for further work in this area.

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