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Gut Microbiome Remodeling Across CKD Etiologies Reveals Ecological Imbalance Signatures Linked to Kidney Injury

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Case Study : Background: Gut microbiome dysbiosis has been implicated in chronic kidney disease (CKD), but findings remain inconsistent due to heterogeneous methodologies and patient populations. Etiology-specific microbial signatures across biopsy-confirmed CKD subtypes remain poorly characterized. We aimed to systematically characterize etiology- and severity-dependent gut microbiome remodeling in biopsy-confirmed CKD. Methods: A total of 435 CKD patients (45.1% male; age 49 [37.0–60.0] years) and 51 healthy donors (HD; 47.1% male; age 49 [37.5–56.0] years) were enrolled. Biopsy-confirmed CKD diagnoses included IgA nephropathy (IgAN, n=231), lupus nephritis (LN, n=12), diabetic nephropathy (DMN, n=56), minimal change disease (MCD, n=51), and membranous nephropathy (MN, n=85). Disease stage and severity were stratified by estimated glomerular filtration rate (eGFR). Additional clinical variables, including urine protein-to-creatinine ratio (UPCR), were collected. Shotgun metagenomic sequencing was conducted on stool samples to generate microbial taxonomic and functional profiles. Diversity analyses and multivariable association models were performed to identify microbial features associated with kidney function and other clinical variables. Results: Significant gut microbiome differences were observed across CKD etiologies and disease severity. Multiple taxa were associated with kidney function and disease etiology, with Eubacterium abundance consistently correlating with CKD subtype, severity, and progression (adjusted $P < 0.05$). A reduction in Prevotella was observed in most CKD subtypes. Etiology-specific signatures were particularly evident in IgAN, which showed enrichment of sulfur-metabolizing and H₂S-producing pathobionts including Bilophila and members of the Desulfovibrionaceae family. The microbial balance between Desulfovibrionaceae and Eubacterium, as well as between Eubacterium and Bacteroides, was consistently associated with UPCR. Preserved kidney function was associated with microbial pathways involved in amino acid and nucleotide metabolism, vitamin biosynthesis, the urea cycle, and central energy metabolism. Conclusions: These findings reveal etiology- and severity-dependent gut microbiome remodeling in biopsy-confirmed CKD, identifying Eubacterium-centered ecological imbalance as a candidate biomarker of kidney injury and disease progression independent of etiology.