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# The Gut-Kidney Axis in Type 2 Diabetes: A Comprehensive Microbiological Perspective on Pathogenesis and Novel Therapeutic Avenues

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**Abstract**

**Background:** The human gut microbiome is a dynamic ecosystem, playing a central role in host metabolism. In Type 2 Diabetes, gut dysbiosis-characterized by a reduction in microbial diversity and function-is now considered not only a consequence but also a major contributor to the development of complications such as Diabetic Kidney Disease. Indeed, the gut-kidney axis represents a key route through which microbial metabolites affect renal health.

**Aim:** The aim of this review is to collate recent evidence (2015-2025) on the mechanisms through which gut dysbiosis drives DKD pathogenesis and to assess novel, microbiome-targeted therapeutic strategies.

**Methods:** Extensive literature review focused on microbial taxonomic and functional shifts in T2D and DKD. Review design uses a microbiological approach to dissect the gut-kidney axis, focusing on specific microbial metabolites and pathways.

**Results:** Diabetic dysbiosis is characterized by the depletion of saccharolytic, SCFA-producing bacteria and the expansion of proteolytic pathobionts, which produce uremic toxins, such as indoxyl sulfate and TMAO. These metabolites foster renal inflammation, oxidative stress, and fibrosis. Therapeutic approaches using pre/probiotics, FMT, and microbial enzyme inhibitors have shown promising potential for the restoration of microbial ecology and mitigation of renal injury.

**Conclusion:** The gut-kidney axis requires a deep microbiological understanding for the elaboration of novel biomarkers and ecologically-based interventions, with the aim of reducing the burden of DKD in the T2D population.

**Keywords:** Gut-Kidney Axis, Diabetic Kidney Disease, Gut Microbiome, Dysbiosis, Microbial Metabolites.

## Introduction

The human gastrointestinal tract is a host to an immensely diverse collection of microorganisms known as the gut microbiome, which co-evolved with humans to form a mutualistic relationship. Advances in high-throughput sequencing technologies, particularly 16S rRNA gene sequencing and shotgun metagenomics, have dramatically changed our view on this complex ecosystem and its profound influence on human health and diseases. Type 2 Diabetes represents a global pandemic affecting hundreds of millions worldwide, where its pathogenesis extends beyond traditional metabolic pathways into significant alterations in gut microbial ecology. The gut microbiome of individuals with T2D consistently demonstrates reduced phylogenetic diversity, an altered Firmicutes-to-Bacteroidetes ratio, decreased abundance of butyrate-producing bacteria, and an expansion of various opportunistic pathogens and conditionally pathogenic taxa. This dysbiotic configuration is not merely an associative finding; it mechanistically contributes to disease pathogenesis through multiple pathways, including impaired SCFA signaling, increased gut permeability, chronic systemic inflammation, and altered bile acid metabolism.

Diabetic Kidney Disease (DKD) represents one of the most serious microvascular complications of T2D, with ~40% of patients affected; it is the leading cause of end-stage renal disease globally. The gut-kidney axis has emerged as a critical framework for understanding the bidirectional relationship between the gut microbial community and renal health. This axis represents a complex network of communication wherein gut-derived microbial metabolites and structural components directly influence renal physiology, while the decline in renal function reciprocally alters the colonic environment and microbial community structure. The uremic milieu of advancing CKD creates a selective pressure that enriches for bacterial taxa capable of utilizing nitrogenous waste products for nutrition, further exacerbating dysbiosis and creating a vicious cycle of metabolite-mediated renal damage (Figure 1).


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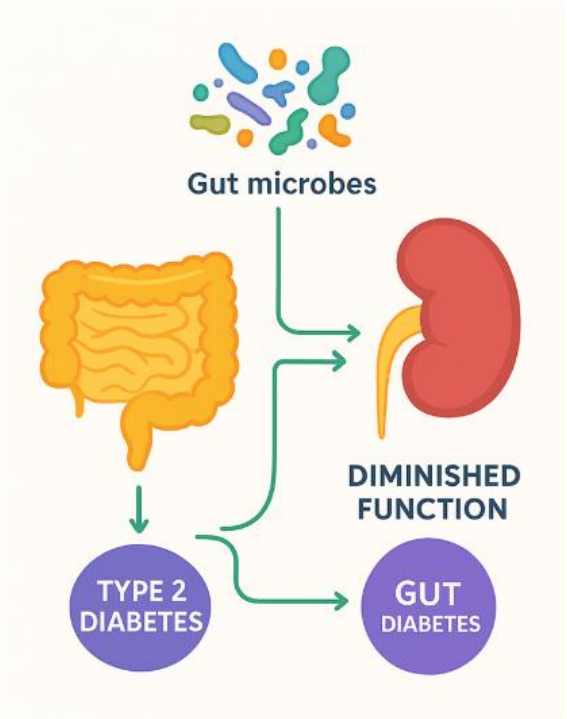


**Figure 1: The Gut–Kidney Axis in Type 2 Diabetes**

The current review will discuss specific microbial taxa, their encoded enzymatic pathways, and the resulting metabolic outputs participating in DKD pathogenesis and progression. Subsequently, the review will delve into state-of-the-art therapeutic strategies directed at the manipulation of this microbial ecosystem, progressing from broad ecological interventions through dietary modification and FMT to precisely targeted approaches such as defined microbial consortia and small-molecule inhibitors of specific microbial enzymes. Integration of this detailed microbiological perspective is essential to advance beyond observational correlations to causative microbiota-based management strategies for DKD.

**Microbial Pathogenesis: Taxonomic Shifts and Functional Consequences in DKD**

The shift from a healthy, symbiotic gut microbiome to a diabetogenic and nephrotoxic ecosystem involves specific, reproducible changes in microbial population dynamics and their collective metabolic output, with direct consequences for renal health (Figure 2).

**Ecological Collapse: Loss of Microbial Diversity and SCFA Producers**

A key attribute of a healthy, resilient gut ecosystem is high phylogenetic diversity, which provides functional redundancy and stability against environmental perturbations (Lloyd-Price et al., 2017). In T2D and its renal complication, DKD, this diversity is significantly and consistently reduced, pointing to an ecologically compromised state (Jiang et al., 2025). Crucially, this collapse often involves the specific depletion of key SCFA-producing genera within the *Firmicutes* phylum, particularly those belonging to the Lachnospiraceae and Ruminococcaceae families, such as *Roseburia*, *Faecalibacterium prausnitzii*, *Eubacterium rectale*, and *Anaerostipes* (Tilg et al., 2020). These taxa represent primary degraders of complex dietary fibers and are major producers of the SCFAs butyrate, acetate, and propionate. Butyrate, in particular, serves as the preferred energy source for colonocytes, and its deficiency has been directly linked to compromised intestinal epithelial integrity through dysregulation of tight junction proteins, for example, occludin and ZO-1, leading to increased gut permeability ("leaky gut") (Parada Venegas et al., 2019). The loss of these beneficial, symbiotic taxa represents a critical failure in the ecosystem's ability to maintain host-microbe homeostasis, thereby creating an ecological niche for pathobionts to expand and exert their detrimental effects.

**Expansion of Proteolytic Pathobionts and Uremic Toxin Production**

With the decline in saccharolytic fermentation upon the loss of fiber-utilizing specialists, proteolytic fermentation is also a more dominant metabolic pathway of the gut ecosystem (Wu et al., 2020). Ecological changes include the expansion of bacterial families capable of fermenting the aromatic amino acids, including Enterobacteriaceae such as *Escherichia coli*, and species within genera such as *Clostridium* (e.g., *C. difficile*), Bacteroides (e.g., B. fragilis), and *Fusobacterium* (Gryp et al., 2020). These proteolytic pathobionts contain specific enzymatic machinery, including tryptophanase, which catalyzes the conversion of tryptophan to indole, and phenolic acid decarboxylases, which produce p-cresol, leading to the generation of uremic toxin precursors indole and p-cresol (Saito et al., 2018). These are then metabolized by host hepatic enzymes (sulfotransferases and cytochrome P450s) upon absorption into the portal circulation into the protein-bound uremic toxins Indoxyl Sulfate (IS) and p-Cresyl Sulfate (PCS) (Lim et al., 2021). Such an accumulation of IS and PCS in the context of CKD may directly promote renal tubular oxidative stress through the activation of NADPH oxidases, stimulate the pro-fibrotic phenotype through the activation of the TGF-β1/Smad3 pathway, and exacerbate endothelial dysfunction, thereby acting as a direct mechanistic link between specific microbial metabolic pathways and the progression of renal pathology (Ito & Yoshida, 2014; Wu et al., 2020).

**The TMAO pathway: a metagenomic risk factor for renal fibrosis**

The nephrotoxic metabolite TMAO is produced via microbial metabolism of dietary quaternary amines, mainly phosphatidylcholine, choline, and L-carnitine, abundant in animal-based foods (Tang et al., 2019). The first and rate-limiting reaction is mediated by microbial TMA lyases,

enzymes encoded by the cutC/D gene clusters specific for choline and cntA/B for carnitine, present in a subset of gut bacteria (Roberts et al., 2018). Several metagenomic and metatranscriptomic studies have documented that in DKD patients, there is an enriched abundance and expression of microbial genes responsible for TMA synthesis, often carried by taxa such as *Emergencia timonensis*, *Proteus* spp., *Providencia* spp., and certain species belonging to the *Anaerococcus*, *Prevotella*, and *Desulfovibrio* genera (Romano et al., 2015; Skye et al., 2018). This represents a direct "gain of function" in the diabetic gut microbiome in that an enhanced genetic capacity for TMA production, upon exposure to precursor-rich diets, translates into higher systemic levels of TMAO. In turn, high levels of circulating TMAO have been strongly and independently related to rapid renal function decline and cardiovascular events in cohorts with T2D (Tang et al., 2019). Specifically, TMAO promotes renal fibrosis and inflammation by activating the NLRP3 inflammasome in tubular cells of the renal cortex, by triggering endoplasmic reticulum stress, and by stimulating pro-fibrotic signaling pathways, directly linking microbial metabolism to renal tissue damage.

**Mucin Degradation and Barrier Dysfunction: The Paradox of Akkermansia**

*Akkermansia muciniphila*, a mucolytic bacterium from the Verrucomicrobia phylum, represents a very fascinating paradox in microbiome research (Cani & de Vos, 2017). In general, in metabolically healthy states, its abundance is related to a thick mucus layer and improved metabolic parameters, probably via its ability to promote mucus turnover and the production of beneficial metabolites (Wu et al., 2023). However, in established inflammation and severe dysbiosis, such as in advanced T2D and DKD, relative overgrowth and/or changed activity may contribute to pathological erosion of the mucosal barrier (Everard et al., 2013). Degradation of protective mucin glycoproteins by *A. muciniphila* and other mucin-degrading bacteria may allow the translocation of immunogenic molecules, such as LPS, into systemic circulation, thereby potentiating chronic low-grade inflammation key driver of insulin resistance and renal injury (Plovier et al., 2017). The role of mucin-degrading taxa in DKD progression remains an active area of investigation and illustrates an important principle, which is that the impact of a given bacterial species is very much context-dependent based on the overall structure and functional status of the microbial community (Derrien et al., 2011).

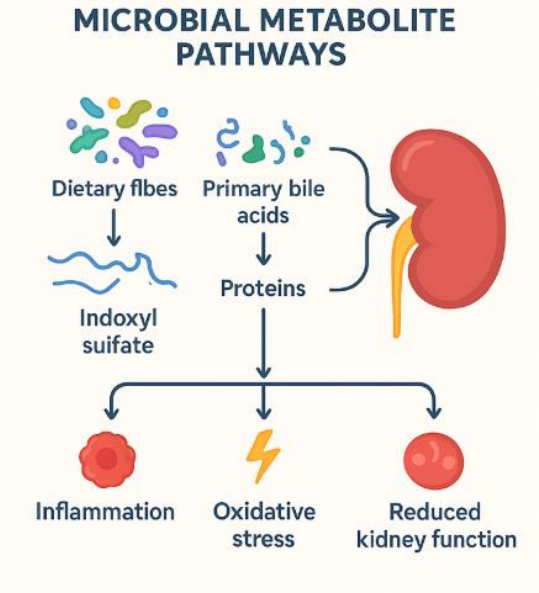


**Figure 2: Microbial Metabolite Pathways Contributing to Diabetic Kidney Disease**

**The Microbiome as a Diagnostic and Prognostic Tool in DKD**

The structure, composition, and functional potential of the gut microbiota now provide unparalleled opportunities for the discovery of novel diagnostic and prognostic biomarkers in DKD, beyond traditional clinical parameters (Table 1).

**Table 1: Microbial Taxa, Functional Genes, and Metabolites as Biomarkers in Diabetic Kidney Disease**

| Biomarker Category | Specific Microbial Feature | Microbiological and Clinical Interpretation | Key References |
|---|---|---|---|
| **Taxonomic Biomarker** | ↓ *Faecalibacterium prausnitzii* | Loss of a primary butyrate-producer; an indicator of reduced symbiotic function and anti-inflammatory capacity; correlates with disease severity. | Wu et al., 2021; Jiang et al., 2025; Tamanai-Shacoori et al., 2017 |
| | ↑ *Enterobacteriaceae* (e.g., *Escherichia coli*) | Expansion of proteolytic, LPS-producing pathobionts; associated with increased inflammation and uremic toxin production. | Zeng et al., 2023; Gryp et al., 2017; Sampaio-Maia et al., 2016 |
| **Functional Gene Biomarker** | ↑ Abundance of *cutC/D* and *cntA/B* genes | Increased metagenomic capacity for TMA production, a direct | Romano et al., 2015; Roberts et al., 2018; Skye |

| | | | |
|---|---|---|---|
| | | precursor to the pro-fibrotic metabolite TMAO, predicts renal function decline. | et al., 2018 |
| | ↓ Abundance of butyrate kinase (*buk*) and butyryl-CoA:acetate CoA-transferase genes | Reduced genetic potential for butyrate synthesis, correlating with impaired gut barrier function and systemic inflammation. | Xiang et al., 2023; Vital et al., 2017 |
| **Metabolomic Output** | Elevated Fecal/Serum Indole and p-Cresol | Direct functional readout of proteolytic bacterial activity; strong predictors of DKD progression and mortality. | Wu et al., 2020; Ito & Yoshida, 2014; Saito et al., 2018 |
| | Elevated Plasma TMAO | Integrative measure of dietary intake, microbial TMA lyase activity, and host hepatic FMO3 function; an independent risk factor for CKD progression. | Tang et al., 2019; Zhang et al., 2020; Organ et al., 2016 |

The real power of a microbiological approach to biomarker discovery, however, lies in the progression from descriptive taxonomy towards a functional understanding of the community. Shotgun metagenomics enables the quantitative assessment of microbial gene families and metabolic pathways, enabling a direct estimate of the community's potential to produce injurious (e.g., TMA, p-cresol) or protective (e.g., butyrate) metabolites. This functional potential, when combined with the direct measurement of resultant microbial metabolites in circulation, yields a comprehensive and mechanistic perspective of gut ecosystem activity and its direct influence on host renal physiology. A multi-omics profile-integrating metagenomic, metabolomic, and clinical data offers great promise toward stratifying T2D patients by their individual "microbiome risk" for rapid DKD progression.

**Therapeutic Modulation of the Gut Ecosystem in DKD**

The recognition of the gut microbiome's role in DKD pathogenesis has catalyzed the development of numerous therapeutic strategies to restore a healthy microbial ecology, ranging from broad, community-wide interventions to highly targeted precision approaches (Table 2).

**Prebiotics**

Prebiotics were originally defined as substrates that are selectively utilized by host microorganisms, conferring a health benefit. Resistant starch, inulin, fructo-oligosaccharides, and arabinoxylan are paradigm examples that selectively stimulate the growth and activity of beneficial SCFA-producing bacteria, particularly within the *Bifidobacterium*, *Lactobacillus*, and *Roseburia* genera. By shifting the fundamental nutrient base within the colon away from proteolysis and toward saccharolysis, prebiotics can effectively suppress the growth of proteolytic pathobionts and reduce the production of uremic toxins, including IS and PCS. Furthermore, the resultant increase in SCFA production, particularly butyrate, directly reinforces the gut barrier by upregulating tight junction protein expression and exerting potent anti-inflammatory effects on the host immune system. Clinical trials to date, while small in duration and size, have demonstrated that prebiotic supplementation can improve glycemic control, reduce inflammatory markers, and modestly improve renal parameters in patients with T2D and early DKD.

**Probiotics and Synbiotics**

Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host (Hill et al., 2014). While traditional probiotics (e.g., *Lactobacillus* and *Bifidobacterium* strains) have shown modest success in improving metabolic parameters and reducing uremic toxins in small-scale human studies, the future lies in "next-generation probiotics" or live biotherapeutic products (LBPs) that are selected based on specific, mechanism-based functions (Cunningham et al., 2021). These may include butyrate-producing strains like *Faecalibacterium prausnitzii* or *Anaerobutyricum soehngenii*, or mucin-friendly strains like *Akkermansia muciniphila*, which are currently under investigation in clinical trials for metabolic disease (Depommier et al., 2019; Gilijamse et al., 2020). Synbiotics, which combine probiotics with prebiotics, are designed to create a synergistic effect by providing both the beneficial microbes and the specific substrates they require to successfully engraft and persist within the competitive gut environment (Tonucci et al., 2017; Swanson et al., 2020).

**Table 2: Microbiome-targeting therapeutic interventions in diabetic kidney disease**

| Intervention Type | Mechanism of Action | Microbiological Impact | Example References |
|---|---|---|---|

| | | | |
|---|---|---|---|
| **Prebiotic (Resistant Starch)** | Fermented by saccharolytic bacteria to produce SCFAs; lowers colonic pH. | ↑ *Bifidobacterium*, ↑ *Roseburia*; ↓ pH suppresses proteolytic bacteria; ↑ fecal butyrate. | Xiang et al., 2023; Baxter et al., 2019 |
| **Synbiotic** | Probiotic + prebiotic, designed for a synergistic effect. | Improved engraftment and persistence of probiotic strain; sustained modulation of community structure and function. | Tonucci et al., 2017; Swanson et al., 2020; Naseri et al., 2023 |
| **Fecal Microbiota Transplantation (FMT)** | Introduction of a complete, diverse microbial community from a healthy donor. | Global restoration of alpha-diversity and functional capacity; most radical ecological reset. | Kootte et al., 2017; Zeng et al., 2023; van Nood et al., 2013 |
| **Microbial Enzyme Inhibitor (e.g., DMB, IMC)** | Non-lethally inhibits microbial TMA lyase (*cutC*) activity. | ↓ TMA and TMAO production without affecting bacterial viability; targeted functional blockade of a specific pathway. | Roberts et al., 2018; Organ et al., 2016; Skye et al., 2018 |

**Fecal Microbiota Transplantation (FMT)**

FMT stands for the most straightforward and effective method to correct severe dysbiosis by introducing a stable, diverse, and functionally robust ecosystem from a rigorously screened healthy donor (Gupta et al., 2016). In preclinical animal models of DKD, FMT from healthy controls has been shown to reverse dysbiosis, lower circulating levels of IS and TMAO, reduce systemic inflammation, and improve histological markers of renal injury and fibrosis (Zeng et al., 2023; Zhang et al., 2020). In human studies for metabolic syndrome, FMT from lean donors has transiently demonstrated improvement in insulin sensitivity, with efficacy often linked to the baseline microbial diversity of the recipient (Kootte et al., 2017; Yu et al., 2020). Although its application for DKD in humans is still experimental, it appears particularly promising for patients with severe, intractable dysbiosis, yet substantial challenges regarding standardization, long-term safety, donor screening, and regulatory approval remain unresolved (Smits et al., 2013).

**Pharmacomicrobiomics: Targeting the Microbial Metabolome and Enzymatic Machinery**

Interest in this rapidly emerging area has two major interrelated fronts: 1) to what extent do existing active pharmaceutical agents, such as metformin and SGLT2 inhibitors, exert their therapeutic mechanisms with a modification of the gut microbiome, and 2) the development of novel drugs with direct action at the level of microbial function. For example, metformin treatment is associated with an increase of *Akkermansia muciniphila* and SCFA-producing bacteria, which could be responsible for the improvement in glucose-lowering and anti-inflammatory effects (Wu et al., 2020; de la Cuesta-Zuluaga et al., 2017). SGLT2 inhibitors seem to induce favorable changes in gut microbial structure that may add to the well-documented cardiorenal benefits of this drug class (Lee et al., 2018; Matsui et al., 2023). The fortuitous impact of known drugs aside, there is intense interest in developing a new family of drugs targeted to the gut-kidney axis. The most developed examples are inhibitors of TMA lyase, including 3,3-dimethyl-1-butanol (DMB) and the far more potent iodomethylcholine (IMC), which non-lethally block the microbial cutC enzyme, leading to a sharp decline in TMAO production and greatly reduced renal fibrosis and inflammation in animal models without broad-spectrum antimicrobial effects (Roberts et al., 2018; Organ et al., 2016). Therein lies a paradigm shift towards precision medicine that targets microbial "virulence factors" or metabolic pathways with little collateral damage to overall community structure.

**Conclusion and Future Perspectives**

By providing a detailed microbiological perspective on the gut-kidney axis, our understanding of DKD pathogenesis has moved from a model focused solely on host biochemistry and hemodynamics to one where host-microbe ecology lies centrally in determining disease progression. In brief, the development and progression of DKD are promoted by a collapse in microbial diversity, the loss of keystone SCFA-producing species, and the expansion of pathobionts with specific enzymatic capabilities that produce a cascade of nephrotoxic metabolites, including IS, PCS, and TMAO. Future studies have to prioritize the shift from observational association to mechanistic causation. This will require sophisticated approaches, such as the use of gnotobiotic (germ-free) animal models colonized with defined microbial consortia derived from DKD patients, for direct validation of the pathogenic potential of specific microbial communities and their metabolites (Kashyap et al., 2017; Relman, 2020).

From a clinical translation standpoint, the holy grail is the development of personalized microbiota management. For example, selection of the most effective prebiotic fiber, probiotic strain, or dietary pattern based on a patient's baseline metagenomic and metabolomic profile could provide a personalized Mediterranean, low-TMA precursor diet (Zeevi et al., 2019; Asnicar et al., 2021). Second, continued discovery and development of more potent,

specific, safe microbial enzyme inhibitors will open an entirely new pharmacopeia aimed squarely at disrupting noxious microbiome-derived pathways without compromise of the salutary functions of the ecosystem (Fischbach, 2018). The effective management of DKD in the 21st century will inescapably involve the sophisticated management of the gut microbial ecosystem, rendering clinical microbiology and microbial ecology key disciplines for the modern nephrologist, endocrinologist, and translational researcher.

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