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Review

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Gastrointestinal Dysbiosis and Resistant Hypertension in Chronic Kidney Disease: Mechanisms, Clinical Evidence, and Therapeutic Perspectives

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ABSTRACT

Resistant hypertension (RH) is disproportionately prevalent in patients with chronic kidney disease (CKD) and is strongly associated with accelerated cardiovascular morbidity and CKD progression. Emerging evidence suggests that gastrointestinal dysbiosis may represent a modifiable contributor to RH through multiple converging mechanisms, including accumulation of protein-bound uremic toxins, impaired short-chain fatty acid signaling, heightened systemic inflammation and oxidative stress, sympathetic activation, altered bile acid metabolism, increased intestinal permeability, and microbe–drug interactions that attenuate antihypertensive efficacy. This review synthesizes mechanistic, clinical, and translational evidence linking gut dysbiosis to RH in CKD, with a focus on therapeutic strategies and unmet needs. Finally, critical research gaps were outlined and a pragmatic agenda was proposed for translational studies and precision microbiome-guided interventions aimed at improving blood pressure control and cardiovascular-renal outcomes.

Keywords: Chronic kidney disease, dysbiosis, gut microbiota, resistant hypertension, uremic toxins

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INTRODUCTION

Hypertension affects the majority of patients with chronic kidney disease (CKD) and frequently demonstrates treatment resistance, defined as uncontrolled blood pressure (BP) despite adherence to ≥3 antihypertensive agents, including a diuretic, or the requirement for ≥4 agents.[1] Contemporary analyses indicate that, after accounting for white-coat effect and nonadherence, the prevalence of resistant hypertension (RH) is approximately two- to threefold higher in patients with CKD compared with the general hypertensive population and increases progressively with declining estimated glomerular filtration rate and higher levels of albuminuria.[2,3]

The emerging concept of the "gut–kidney–heart" axis links dysbiosis and uremia through microbial and barrier dysfunction that amplify vascular injury and neurohormonal activation. Recent science advisories and narrative reviews support a potential mechanistic contribution of gut microbes and their metabolites to BP regulation.[4,5]

This review critically appraises mechanistic and clinical evidence linking gastrointestinal dysbiosis to RH in CKD, emphasizing areas of robust evidence, persisting uncertainties, and translational implications. Gut-derived metabolites, short-chain fatty acid (SCFA) signaling, neurohumoral crosstalk, intestinal barrier dysfunction, salt sensitivity, and microbe-drug interactions, with particular attention to study design, bias, and reproducibility were examined. Finally, therapeutic implications and research priorities were discussed for microbiome-guided interventions in RH.

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This review integrates evidence on the microbiome, RH, and CKD to provide a translational perspective on gut-targeted strategies.

MATERIAL AND METHODS

This review was conducted as a narrative synthesis of the current evidence. Relevant studies were identified through searches of PubMed, Scopus, and Web of Science for articles published between 2015 and 2025. The search strategy combined the following key terms and Boolean operators: "chronic kidney disease," "CKD," "resistant hypertension," "refractory hypertension," "gut microbiota," "dysbiosis," "uremic toxins," and "TMAO." Studies examining associations between gut microbiota, microbial metabolites, or dysbiosis and RH in adults with CKD were included. Case reports, non-peer-reviewed sources, pediatric populations, and studies without microbiota or BP assessment were excluded. The strength of evidence was qualitatively appraised based on design, sample size, and reproducibility.

Pathophysiological Basis of Resistant Hypertension in Chronic Kidney Disease

Established drivers of RH in CKD include sodium retention with impaired natriuresis, renin-angiotensin-aldosterone system (RAAS) and sympathetic overactivity, arterial stiffness, hyperaldosteronism, obstructive sleep apnea (OSA), and medication underdosing/nonadherence. Dysbiosis may intersect with these pathways through metabolite-mediated inflammation, endothelial dysfunction, and neurohumoral effects, potentially explaining residual hypertension despite guideline-directed therapy[3] (Table 1).

MAIN POINTS

- Gastrointestinal dysbiosis is plausibly implicated in resistant hypertension (RH) among patients with chronic kidney disease (CKD) through mechanisms involving uremic toxin accumulation, short-chain fatty acid deficiency, systemic inflammation, and neurohumoral dysregulation.
- Current evidence remains predominantly associative and is limited by heterogeneous RH phenotyping, cross-sectional study designs, and confounding effects of kidney function and dietary patterns.
- Precision phenotyping and standardized methodologies for microbiome assessment are essential to delineate reproducible microbial signatures and establish causal relationships.
- Emerging interventions targeting the gut-kidney-heart axis, such as dietary modification, prebiotic and probiotic supplementation, and strategies to reduce uremic toxin burden, demonstrate potential but require adequately powered, CKD-specific clinical trials with hard cardiovascular and renal endpoints.
- Integrated multi-omics approaches and translational research efforts are needed to advance microbiome-informed, personalized therapeutic strategies aimed at improving blood pressure control and cardiovascular-renal outcomes.

Resistant hypertension in CKD is a multifactorial phenomenon that reflects both disease-specific alterations in kidney physiology and systemic cardiovascular changes (Figure 1). Several mechanisms are consistently implicated:

Sodium Retention and Volume Overload

Impaired natriuresis is a hallmark of reduced nephron mass. Even modest dietary sodium intake may exceed excretory capacity in moderate-to-advanced CKD, resulting in extracellular fluid expansion and impaired diuretic responsiveness. Sodium retention also promotes vascular stiffness and blunts antihypertensive efficacy. Clinical studies confirm that dietary sodium restriction significantly lowers BP and reduces the prevalence of apparent resistance in CKD cohorts.[6] Persistent extracellular volume overload, particularly in the context of suboptimal loop diuretic dosing, remains a leading and potentially correctable cause of pseudo-resistance.[7]

Sympathetic Nervous System Overactivity

Chronic kidney disease is associated with chronic sympathetic activation, partly mediated by afferent signaling from diseased kidneys, chemoreceptor sensitization, and impaired baroreflex function.[8] Microneurography and plasma catecholamine studies demonstrate heightened sympathetic nerve activity across CKD stages, correlating with RH and left ventricular hypertrophy. Kidney denervation trials in RH suggest partial BP reductions, though efficacy in advanced CKD remains under investigation.

Renin-Angiotensin-Aldosterone System Activation

Despite frequent prescription of ACE inhibitors or angiotensin 2 receptor blockers, residual RAAS activation persists in CKD and contributes to salt-sensitive hypertension and vascular remodeling.[9] Mineralocorticoid receptor antagonists (MRAs) have demonstrated significant additional BP lowering in RH, including CKD subsets, but risk of hyperkalemia complicates broad adoption.[10]

Vascular Stiffness and Endothelial Dysfunction

Arterial stiffness increases with CKD progression due to medial calcification, advanced glycation, and chronic inflammation.[11] Pulse wave velocity is an independent predictor of RH and cardiovascular outcomes.[12] Endothelial dysfunction, reflected in impaired nitric oxide bioavailability, synergizes with sympathetic and RAAS-mediated vasoconstriction to sustain elevated BP.[13]

Secondary Causes and Comorbidities

Obstructive sleep apnea, obesity, diabetes, and hyperaldosteronism are overrepresented in CKD and compound treatment resistance.[14] Diagnostic vigilance for secondary contributors is warranted, particularly in patients requiring ≥4 drugs without optimal control.[15]

Pseudo-Resistance: White-Coat Effect and Nonadherence

Up to one-third of apparent RH may represent white-coat hypertension when assessed by ambulatory BP monitoring.[16]

Table 1. Pathophysiological Links Between Gastrointestinal Dysbiosis and RH in CKD

Mechanism	Microbial/Metabolite Involvement	Effect on Blood Pressure
Uremic toxins	Indoxyl sulfate, p-cresyl sulphate	Endothelial dysfunction, arterial stiffness, renal fibrosis
TMAO pathway	TMAO from choline/carnitine metabolism	Vascular inflammation, fibrosis, impaired diuresis
SCFA depletion	Reduced acetate, propionate, butyrate	Impaired vasodilation, increased RAAS and sympathetic tone
Barrier dysfunction	Increased gut permeability, endotoxin translocation	Chronic inflammation, oxidative stress
Microbe-drug interaction	Enzymatic hydrolysis of ACE inhibitors by gut bacteria	Reduced antihypertensive efficacy

ACE, angiotensin-converting enzyme; CKD, chronic kidney disease; RAAS, renin–angiotensin–aldosterone system; SCFA, short-chain fatty acids; TMAO, trimethylamine N-oxide.

Similarly, biochemical assays and electronic monitoring consistently demonstrate that nonadherence is underrecognized yet prevalent. Distinguishing true from pseudo-resistance is crucial for both research and clinical management.[17]

Although sodium retention, RAAS overactivity, and sympathetic activation are well-established mechanisms, these factors alone do not fully explain the disproportionately high prevalence of RH in CKD. Moreover, standard therapies directed at these pathways, including loop diuretics, RAAS blockade, MRA, and continuous positive airway pressure for OSA, achieve only partial resolution of resistance. These limitations suggest that additional mechanisms, possibly arising outside the kidney, contribute to the pathophysiology of RH. This recognition provides a rationale for investigating gastrointestinal dysbiosis as a potential contributor to treatment resistance.[18]

Dysbiosis in Chronic Kidney Disease: Features and Consequences

Chronic kidney disease is associated with reduced microbial diversity, expansion of proteolytic and urease-expressing taxa, and depletion of fiber-fermenting commensals. These shifts favor production and retention of uremic solutes (indoxyl sulfate (IS), p-cresyl sulfate (PCS)), trimethylamine N-oxide (TMAO), and other metabolites while reducing beneficial SCFAs. Updated reviews describe disease-specific microbial signatures across CKD etiologies and stages.[19]

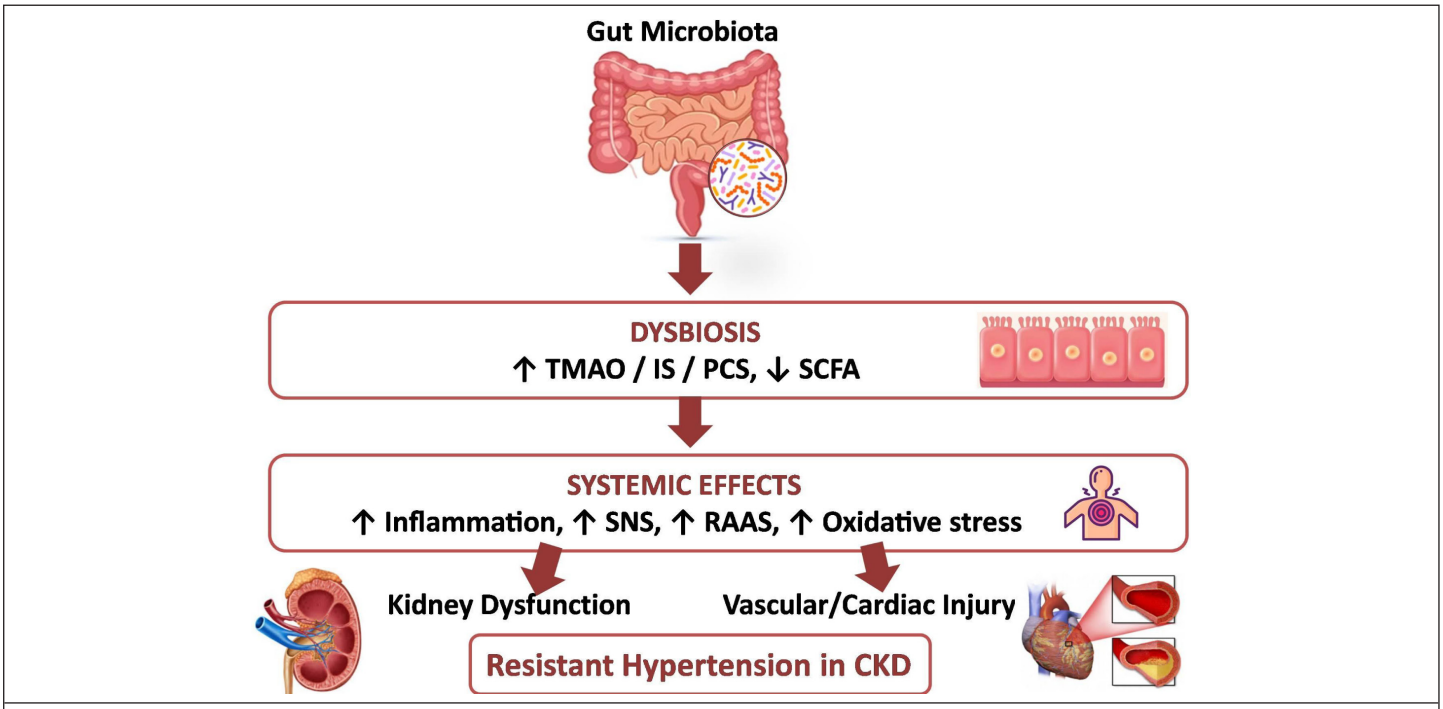

Figure 1. The gut–kidney–heart axis linking dysbiosis to resistant hypertension in chronic kidney disease (CKD). Schematic representation of the gut–kidney–heart axis linking dysbiosis to resistant hypertension in CKD. Intestinal dysbiosis decreases short-chain fatty acid (SCFA) production and increases trimethylamine-N-oxide (TMAO) and uremic toxins (indoxyl sulfate, p-cresyl sulfate), promoting inflammation, oxidative stress, renin–angiotensin–aldosterone system (RAAS) and sympathetic activation, and endothelial dysfunction. Chronic kidney disease further worsens dysbiosis, creating a feed-forward loop.

Mechanistically, dysbiosis contributes to:

- Increased intestinal permeability with translocation of endotoxin and microbial products, fueling systemic inflammation and oxidative stress.[20]
- Altered fermentation with reduced SCFA and impaired signaling through G-protein-coupled receptors and Olfr78, affecting vascular tone and renal hemodynamics.[21]
- Uremic solute accumulation due to reduced renal clearance and protein binding that limits dialytic removal.[22,23]

Mechanistic Links Between Dysbiosis and Resistant Hypertension

Uremic Toxins: Indoxyl Sulfate and p-Cresyl Sulfate

Indoxyl Sulfate and PCS, arising from bacterial metabolism of tryptophan and tyrosine, accumulate early in CKD and exert endothelial, vascular smooth muscle, and renal fibrotic effects that collectively raise BP and stiffen arteries. Their protein-bound nature impairs clearance by conventional dialysis. Experimental and clinical data over the last decade suggest associations with vascular dysfunction and adverse outcomes in CKD.[23,24]

Trimethylamine N-Oxide and Related Metabolites

Trimethylamine N-oxide, produced from microbial conversion of dietary choline/carnitine to TMA and subsequent hepatic oxidation, is consistently linked with CKD progression, hypertension, and cardiovascular disease. Experimental studies indicate that TMAO promotes vascular inflammation and fibrosis, while population-based analyses link elevated TMAO with reduced kidney function and adverse cardiovascular outcomes.[25-27]

Short-Chain Fatty Acid

Short-chain fatty acid (acetate, propionate, butyrate) from fiber fermentation engage vascular and renal receptors to influence renin release, sympathetic activity, and endothelial NO bioavailability. Preclinical studies demonstrate that SCFAs influence vascular tone and renin release through receptor-mediated pathways.[21,22]

Neurohumoral and Immune Crosstalk

Experimental data show that dysbiosis can influence sympathetic activation and salt sensitivity relevant to RH pathophysiology.[28]

Microbe–Drug Interactions

Gut microbes can inactivate or alter exposure to antihypertensives. Experimental data indicate that *Coprococcus comes* can hydrolyze ester ACE inhibitors, diminishing their blood-pressure-lowering effect, while broader microbiome changes may affect the pharmacokinetics and intestinal effects of several drug classes. Such interactions could contribute to interindividual variability in antihypertensive response and warrant further clinical evaluation.[29,30]

Clinical Evidence Linking Dysbiosis to Resistant Hypertension

Direct human evidence in CKD-specific RH remains limited but is gradually expanding. One recent study profiling the gut microbiome and metabolome in RH demonstrated reduced α-diversity and enrichment of specific microbial taxa compared with controlled hypertension, suggesting a dysbiosis signature characteristic of RH.[31,32] Complementary human and animal data consistently support associations between altered microbial composition, metabolite profiles, and BP regulation.[4,5,19,31]

Observational CKD cohorts have linked higher circulating levels of microbial metabolites, particularly TMAO and protein-bound uremic toxins such as IS and PCS, with adverse renal and cardiovascular outcomes.[23-26,33-37] Conversely, SCFA concentrations have been associated with impaired endothelial function, increased sympathetic tone, and higher BP.[21,27,28,33-35] However, causality remains uncertain, as these associations are influenced by reduced renal clearance, dietary intake, and interindividual variability in microbiome composition.[2,25,38-41]

Emerging interventional evidence, although limited, suggests that dietary modulation, probiotics, and toxin-binding agents can beneficially affect microbial composition and metabolite levels, with modest BP improvements.[2,39,42] These data provide translational support for targeting the gut-kidney-heart axis as an adjunct to current antihypertensive therapy, warranting validation in CKD-specific RH trials. As end products of carbohydrate fermentation by diverse gut microbes, SCFA represent a central node of microbial metabolism. Their plasma concentrations reflect both the composition and functional activity of microbial communities.[35] Future research is needed to delineate which specific SCFA molecules and host receptors mediate these physiological effects. In addition, untargeted metabolomics has recently identified other microbiota-derived metabolites that may influence BP beyond SCFA.[36] Among these are uremic toxins previously implicated in RAAS activation and kidney injury in experimental models.[23] Compounds such as PCS, IS, and other aromatic amino acid derivatives have also been proposed to affect host physiology, in part through activation of the aryl hydrocarbon receptor.[37] In CKD cohorts, TMAO and protein-bound uremic toxins have been associated with adverse renal and cardiovascular outcomes, with Mendelian randomization and longitudinal analyses strengthening causal inference for TMAO. Although few clinical trials to date have specifically targeted the microbiome in RH among patients with CKD, the consistency of mechanistic and observational evidence provides a strong rationale for interventional testing.[25,26]

Therapeutic Implications

Understanding the interplay between gastrointestinal dysbiosis and RH in CKD opens opportunities for therapeutic interventions aimed not only at lowering BP but also at modifying the underlying pathophysiological pathways driving cardiovascular and renal risk (Table 2).

Table 2. Therapeutic Strategies Targeting Dysbiosis in RH and CKD

Intervention	Proposed Mechanism	Evidence in CKD/ Hypertension	Limitations	Level of Evidence
High-fiber diet/ Mediterranean diet	Increases SCFA production, reduces uremic toxin precursors	Observational studies show lower BP and inflammation	Risk of hyperkalemia in advanced CKD	Moderate (observational + small RCTs)
Probiotics/ prebiotics/synbiotics	Modulate microbial balance, reduce toxin production	Small clinical trials suggest benefit	Heterogeneity in strains, dose, and endpoints	Low–moderate (pilot trials, preclinical support)
Oral adsorbents	Bind toxin precursors in gut	Mixed results; some reduction in IS/PCS	Limited availability, adherence issues	Moderate (small clinical trials)
SGLT2 inhibitors	May reduce TMAO accumulation, improve renal hemodynamics	Post-hoc analyses suggest benefit	Not directly microbiome-targeted	High (large RCTs, post-hoc analyses)
Fecal microbiota transplantation	Restores eubiotic microbiome	Proof-of-concept studies only	Safety, long-term efficacy not established	Low (preclinical/early clinical)

BP, blood pressure; CKD, chronic kidney disease; IS/PCS, indoxyl sulfate/p-cesyl sulfate; RCT, randomized controlled trial; SCFA, short-chain fatty acids; SGLT2, sodium-glucose cotransporter 2; TMAO; trimethylamine N-oxide.

Dietary Patterns and Fiber

Plant-forward, fiber-rich patterns (e.g., Mediterranean-style) increase luminal fermentable substrates, enhance SCFA production, and may lower BP and systemic inflammation. In CKD, dietary strategies must balance potassium load and protein needs yet can be tailored to safely augment prebiotic fiber.[4]

Probiotics, Prebiotics, and Synbiotics

Targeted pre/pro/synbiotic formulations aim to restore saccharolytic fermentation, increase SCFA, and reduce uremic toxin production. While small trials suggest improvements in surrogate markers, robust, CKD-specific RH outcomes remain to be demonstrated. Ongoing and recent reviews call for standardized strains, dosing, and endpoints.[2]

Modulating Uremic Solutes

Approaches include oral adsorbents and dietary choline/carnitine limitation to reduce TMAO generation, combined with strategies to preserve intestinal barrier integrity. Given the protein-bound nature of IS/PCS, extracorporeal removal is limited, reinforcing the appeal of gut-targeted tactics.[23]

Antihypertensive Selection with Microbiome Awareness

Where feasible, selecting agents less susceptible to microbial hydrolysis (e.g., non-ester ACE inhibitors) may help in suspected microbe-drug interaction-mediated resistance, though clinical validation is pending. Mineralocorticoid receptor antagonists, thiazide-like diuretics (at adequate dose and an estimated glomerular filtration rate (eGFR)), and sodium–glucose cotransporter-2 inhibitors should be used per guidelines; SGLT2 inhibitors may also favorably influence TMAO pathways in some analyses.[26,38]

Emerging/Investigational Strategies

Fecal microbiota transplantation and precision consortia are under early study for hypertension and CKD phenotypes; salt-responsive microbial targets and bacteriophages represent forward-looking avenues. Rigorous CKD-RH trials with standardized microbiome endpoints are needed.[12]

Clinical Management Implications

Although microbiome-targeted therapies remain investigational, current knowledge of gut-kidney-heart interactions already carries clinical relevance. Awareness of dysbiosis-related mechanisms can inform patient care by guiding dietary counseling toward safe increases in fiber intake, avoiding unnecessary antibiotics that disrupt microbial balance, and considering drug-microbiome interactions when selecting or adjusting antihypertensive agents (e.g., avoiding ester-type ACE inhibitors in patients with suspected microbial hydrolysis).

Furthermore, recognizing the potential contribution of dysbiosis to treatment resistance highlights the importance of optimizing volume control, dietary sodium restriction, and adherence verification, which may mitigate pseudo-resistance and improve therapeutic response even before targeted microbiome interventions are available.

Future Directions and Research Gaps

Despite accumulating evidence linking gastrointestinal dysbiosis to the pathogenesis of RH in CKD, the field remains in an early and fragmented stage. Several research gaps must be addressed to translate mechanistic insights into clinically relevant interventions.

Precise Phenotyping of Resistant Hypertension

Most studies investigating the microbiome in CKD rely on office BP measurements without confirmation by ambulatory or home monitoring, and without rigorous assessment of adherence or diuretic adequacy.[39] This heterogeneity blurs the distinction between true RH and pseudo-resistance. Future

studies should adopt standardized definitions of RH consistent with international guidelines, including 24-hour ambulatory BP monitoring, medication adherence verification (biochemical or electronic), and assessment of volume status. Incorporating these elements will enable more accurate distinction between true and pseudo-resistance and improve comparability across cohorts.

Standardization of Microbiome Characterization

The literature remains limited by heterogeneous sequencing platforms, variable bioinformatic pipelines, and inconsistent reporting of dietary and pharmacologic confounders. Future work should use shotgun metagenomic sequencing and targeted metabolomics to improve taxonomic and functional resolution.[40] Integration of multi-omics approaches, combining metagenomics, metabolomics, transcriptomics, and clinical metadata, will help identify reproducible microbial and metabolic signatures specific to CKD-related RH. Establishing standardized sampling protocols, quality control pipelines, and metadata harmonization across centers will be essential for reproducibility.

Establishing Causality

Most available evidence is associative. Elevated levels of TMAO or protein-bound uremic toxins correlate with BP and outcomes, but causality is confounded by reduced renal clearance and reverse causation.[25,41] Longitudinal cohort studies and interventional designs, particularly those manipulating microbial composition or metabolite levels, are needed to disentangle cause from consequence. Mendelian randomization offers promise, but requires validation across diverse ancestries.

Translational Interventions and Clinical Trials

Pilot studies of dietary fiber, prebiotics, probiotics, and toxin-binding agents show promise but are typically small and heterogeneous. Future randomized, multicenter trials should incorporate microbiome stratification at baseline, employ standardized dietary control, and define hard endpoints, including 24-hour ambulatory BP control, CKD progression (eGFR decline or albuminuria), and major adverse cardiovascular events.[42,43] Integration of microbial and metabolomic biomarkers as secondary outcomes will enable mechanistic interpretation of therapeutic responses.

Integration of Multi-Organ Crosstalk

Emerging data suggest that dysbiosis not only alters vascular and renal physiology but also modulates sympathetic activation, immune responses, and drug metabolism. These systemic pathways remain insufficiently characterized in CKD.[25,41-43] Mechanistic studies integrating microbiome analyses with neural, immune, and pharmacokinetic profiling could uncover novel therapeutic targets.

Personalized Therapeutic Strategies

Given the heterogeneity of microbial composition and metabolite profiles among individuals with CKD, a personalized approach is essential. Future research should explore predictive algorithms that link baseline microbiome and metabolomic profiles to therapeutic response, enabling precision nutrition and probiotic strategies tailored to specific microbial phenotypes.

CONCLUSION

The gastrointestinal microbiome represents a promising determinant of RH in CKD. Mechanistic, observational, and translational evidence collectively supports a role for gut-derived metabolites, dysbiosis, and microbe-drug interactions in the pathogenesis of elevated BP and increased cardiovascular risk.

Although current data remain insufficient to inform definitive therapeutic recommendations, future research integrating rigorous RH phenotyping, standardized microbiome assessment, and adequately powered interventional trials is essential to translate these insights into targeted, clinically meaningful interventions.

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