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The role of intestinal microbiota in the pathogenesis of nephropathy in patients with metabolic syndrome; a systematic review

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ABSTRACT

Introduction: The gut microbiota plays a vital role in maintaining metabolic and renal health. Dysbiosis associated with metabolic syndrome contributes to the development of nephropathy through mechanisms involving inflammation and the production of uremic toxins.

Objectives: This study aims to examine the role of the intestinal microbiota in the onset and progression of nephropathy in patients with metabolic syndrome, particularly its impact on renal function.

Methods: A systematic review was conducted covering the period from 2020 to 2025, following PRISMA guidelines. Relevant literature on gut microbiota, nephropathy, and metabolic syndrome was identified through databases including Scopus, Web of Science, Cochrane Library, PubMed, and Europe PMC. The quality of included studies was assessed using the Cochrane Risk of Bias tool and the Newcastle-Ottawa Scale to ensure methodological rigor.

Results: The 16 included studies varied in design, study populations, and duration. All reported a reduction in microbial diversity among patients with chronic kidney disease (CKD) and nephropathy. The presence of *Prevotella* and *Faecalibacterium* was generally associated with improved kidney function, whereas disease progression correlated with higher levels of Proteobacteria and Clostridium. Metabolites such as indoxyl sulfate and p-cresol glucuronide were commonly linked to nephropathy. Interventions such as probiotic supplementation, fecal microbiota transplantation (FMT), and time-restricted feeding (TRF) showed potential in stabilizing the estimated glomerular filtration rate, reducing uremic toxins, and slowing disease progression.

Conclusion: The gut microbiota and its metabolites significantly influence the development and progression of nephropathy in the context of metabolic syndrome. Modulating microbial composition through probiotics and dietary interventions may help restore renal function and mitigate disease advancement.

Registration: This review was conducted in accordance with the PRISMA checklist, and the protocol was registered with PROSPERO (ID: CRD420251053100).

Implication for health policy/practice/research/medical education:
Gut microbiota represents a critical factor in the pathogenesis of nephropathy associated with metabolic syndrome. Targeted interventions such as probiotics, dietary modification, and fecal microbiota transplantation (FMT) may serve as effective adjunct therapies for preserving kidney function. These findings highlight the importance of integrating microbiome-focused strategies into clinical guidelines and educational programs addressing renal disease.

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Review

Introduction

Metabolic syndrome, which incorporates obesity, hyperlipidemia, insulin resistance, and hypertension, poses an enhanced risk for the development of nephropathy, which is an important contributor to chronic kidney disease (CKD) and end-stage renal disease (ESRD) (1,2). Some recent studies have drawn attention to the important role that intestinal microbiota plays in the development of certain metabolic illnesses, such as diabetes and kidney diseases associated with obesity (3,4).

The gut microbiota impacts the metabolism of the host by modifying his/her energy intake, glucose and lipid metabolism, and immune system activity (5-7). Dysbiosis, i.e., the imbalance of the gut microbiota, can cause greater intestinal permeability through the uptake of endotoxins and bacterial products, which in turn leads to inflammation and stress within the body (8-10). The dysregulation of metabolic processes both in the gut and the entire organism is termed 'metabolic dysbiosis (11,12). In this case, the host's gut microbiota produces a large number of metabolites, which are regarded as critical components in the pathogenesis of diabetic nephropathy (13,14). There is ample evidence that supports these claims of enhanced kidney injury in conditions such as diabetic nephropathy (15). Recent studies have also highlighted the potential therapeutic effects of natural plant extracts, which demonstrate antimicrobial and anti-inflammatory properties that could be relevant in the context of metabolic diseases such as nephropathy (16,17). The interaction between gut microbiota and kidney function is complex and mutual (18,19). One aspect is that renal dysfunction changes the renal microbiota composition; however, the changes in microbiota composition can worsen kidney function by producing harmful metabolites and causing systemic inflammation (20). In general, dysbiosis of the gut microbiota underlies a damaging cycle of inflammation, metabolic disruptions, and injury to the kidneys, emphasizing the possibility of microbiome-focused treatment approaches in the management of nephropathy related to metabolic syndrome (21,22). This understanding is important for designing innovative treatment approaches for mitigating the progression of nephropathy among individuals with metabolic syndrome.

This study focuses on understanding the impact of intestinal microbiota in the development of nephropathy in metabolic syndrome patients. The main objectives include assessing how changes in the gut microbiota profile are associated with kidney injury, determining specific microbial metabolites associated with these changes, and evaluating non-pharmacological strategies aimed at the gut microbiome to lessen the severity of nephropathy. Addressing these questions will facilitate the development of microbiome-centered strategies to prevent and treat nephropathy in patients suffering from metabolic syndrome.

Objectives

This review seeks to determine the influence of intestinal microbiota in the development of nephropathy in individuals with metabolic syndrome. The purpose of this study is to pinpoint major microbial changes, inflammatory markers, and their relationships with renal impairment by combining information from previous studies. Grasping these relationships might suggest how to devise microbiota-modulating interventions towards better renal function among patients suffering from metabolic syndrome.

Materials and Methods

Study design and protocol

This systematic review adheres to the guidelines outlined by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (23). This review's primary objective is to explore intestinal microbiota in the pathogenesis of nephropathy in patients with metabolic syndrome. This systematic review aims to synthesize available evidence regarding the association between microbiota composition and the progression of nephropathy in individuals suffering from metabolic syndrome.

Search strategy

Databases including Scopus, Web of Science (WoS), Cochrane Library, PubMed, Embase, Europe PMC, and Google scholar search engine were used for searches utilizing the keywords and their corresponding Medical Subject Headings (MeSH) equivalents. There were no limitations placed on the time or location of studies in the search process, and the search was updated to include articles published until 2025. The keywords used in the search included: "gut microbiota", "gut microbiome", "intestinal microbiota", "microbial dysbiosis", "nephropathy", "chronic kidney disease", "CKD", "diabetic nephropathy", "renal dysfunction", "metabolic syndrome", "insulin resistance", "obesity", "type 2 diabetes", and "hypertension". The keywords were combined using "AND" and "OR" operators.

Inclusion criteria

The criteria for inclusion in the systematic review were limited to publications between 2020 and 2025. Only articles that were subject to peer review and written in English were eligible. Included were studies that reported on the contribution of intestinal microbiota to the development of nephropathy in individuals with metabolic syndrome. Furthermore, only studies with human subjects were eligible, whereas animal studies with inadequate clinical relevance were not. In an effort to promote accessibility and openness of research, free public access studies were used as the primary source. Studies that reported the role of gut microbiota on the

kidney's function in the context of metabolic syndrome and other related disorders were included.

Exclusion criteria

Research that concentrated on other diseases not involving the gut-kidney relationship, as well as those not looking into metabolic syndrome, were excluded. In addition, studies using animal models that did not try to clearly relate their results to human nephropathy were eliminated. Also, other documents were disregarded if they did not conform to the type of document, language, and publication date criteria. Studies designed as case reports, meta-analyses, and systematic reviews were also excluded. Other irrelevant studies, especially those that did not examine the role of the gut microbiota on kidney function and nephropathy, were eliminated from the review. Moreover, those studies that were deficient in sufficient data or clearly lacked any association with microbiota and nephropathy were also removed. Any disagreements between the two authors regarding study exclusion were resolved through discussion and, when necessary, by consultation with a third author who reviewed the articles in question.

PICO component

The research question was formulated according to the PICO framework:

- Population (P): Patients with metabolic syndrome who either have nephropathy or are at risk of developing nephropathy.
- Intervention (I): Modulation of gut microbiota through strategies such as probiotics, dietary modifications, fecal microbiota transplantation (FMT), or time-restricted feeding (TRF).
- Comparator (C): Patients with metabolic syndrome and nephropathy who did not receive microbiota-targeted interventions, or comparisons among different microbiota-modulating strategies.
- Outcome (O): Changes in renal function parameters (e.g., estimated glomerular filtration rate [eGFR], serum creatinine), gut microbiota composition, levels of uremic toxins (e.g., indoxyl sulfate, p-cresol glucuronide), and progression of nephropathy.

Data extraction

Two independent reviewers were involved in data extraction and synthesis, which included gathering details on study design, sample size and population, duration, major findings, microbial taxa, changes in microbiota, improvement in renal function, and relationships with eGFR and creatinine. Consideration was also given to the impacts of metabolic syndrome and the progression of nephropathy. The reviewers' inter-rater reliability of the data extraction was evaluated using Kappa statistics, which showed strong agreement at a Kappa value of 0.82; since, this strategy enhanced the integration of data and the detection of associations between microbiota, nephropathy, and metabolic syndrome.

Quality assessment

The quality assessment of the included studies in this systematic review was conducted using two standardized tools according to study design. For randomized controlled trials (RCTs), the Cochrane Risk of Bias Tool (RoB 2) was conducted (24). This tool evaluates bias across seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. Each domain is judged as having low risk, some concerns, or high risk of bias. The detailed results of this assessment are presented in Table 1. For observational studies, the Newcastle-Ottawa Scale (NOS) was applied (25), which assigns up to 9 stars across three domains: selection (up to 4 stars), comparability (up to 2 stars), and outcome or exposure assessment (up to 3 stars). In this review, studies scoring between 7 and 9 were considered high quality, scores between 4 and 6 were considered moderate quality, and scores between 0 and 3 were considered low quality. Two independent reviewers conducted the assessment, and any disagreements were resolved by discussion or consultation with a third reviewer.

Risk of bias assessment

The risk of bias for the RCTs included in this review was assessed using the Cochrane RoB 2 tool, which evaluates five domains; bias arising from the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result (24). Each domain is judged as low-risk, some concerns, or high risk of bias, and an overall risk of bias is then determined for each study.

Results

The initial search yielded 11 360 records; Scopus (n = 425), WoS (n = 571), Cochrane Library (n = 25), PubMed (n = 342), and Europe PMC (n = 9997). After applying the year filter (2020-2025), the total number of records was reduced to 9294. Additional refinement by document type (Article only) reduced the records to 4529, which was further reduced to 4520 after applying language filters (English) and the open-access filter (n = 4326). After removing duplicates, 4114 records remained. Further exclusion of irrelevant records resulted in 4,060 exclusions, which were due to focusing on unrelated diseases (n = 2842), lacking gut-kidney interaction (n = 852), or being animal model studies (n = 366). The remaining 54 records were assessed, and 38 of them were excluded due to being preclinical studies, narrative reviews, lacking gut-kidney focus, or

insufficient outcome data. The remaining 16 studies (26-41) were considered highly relevant and included in the review (Figure 1).

All five RCTs were judged as having low risk of bias across all domains as shown in Table 1. The quality of observational studies was evaluated using the NOS, which assesses studies based on selection, comparability, and outcome/exposure domains (25). All observational studies were rated as high quality, with scores ranging from 7 to 9. One study received a full score of 9/9, while others scored either 8/9 or 7/9. Most studies demonstrated strong performance in the selection and outcome domains, and full comparability scores were consistently observed as shown in Table 2.

Table 3 summarizes the studies included in the systematic review on the role of intestinal microbiota in the pathogenesis of nephropathy with metabolic syndrome. Aside from the range of designs and sample sizes, the longitudinal studies also differ in duration, which in some cases is as long as 19 years. A number of studies have a particular target population, such as adults who identify as Hispanic/Latino, patients with type 2 diabetes mellitus (T2DM), or individuals with advanced CKD or DN (diabetic nephropathy). Furthermore, other RCTs and observation studies analyze the effects of microbiota on renal function and the progression of nephropathy for a time span of 12 weeks to 6 months.

Table 4 illustrates that the most notable finding from the literature is the decrease in microbiome diversity in the subgroup with low eGFR and fairly common CKD. Certain microbial taxa are correlated to improved kidney function, such as Prevotella, Faecalibacterium, and Oxalobacter, while others, such as Proteobacteria and Clostridium, are associated with enhanced progression of CKD. Apart from these, some other significant biomarkers, such as indoxyl sulfate, arginine, and other specific metabolites, exhibited important relationships with nephropathy. Also, probiotics and dietary interventions, especially TRF, have been shown to be beneficial by improving gut microbiota composition, decreasing uremic toxins, and slowing the progression of ESRD.

Table 5 presents findings from some studies contributing to this systematic review, demonstrating that microbiome-related metabolites, like p-cresol glucuronide and imidazole propionate, are associated with nephropathy and show important relationships with eGFR and serum creatinine. Changes in particular microbial taxa, like Lactobacillaceae and Veillonellaceae, are associated with better kidney health, while some pathogenic taxa like Proteobacteria correspond with the worsening of CKD.

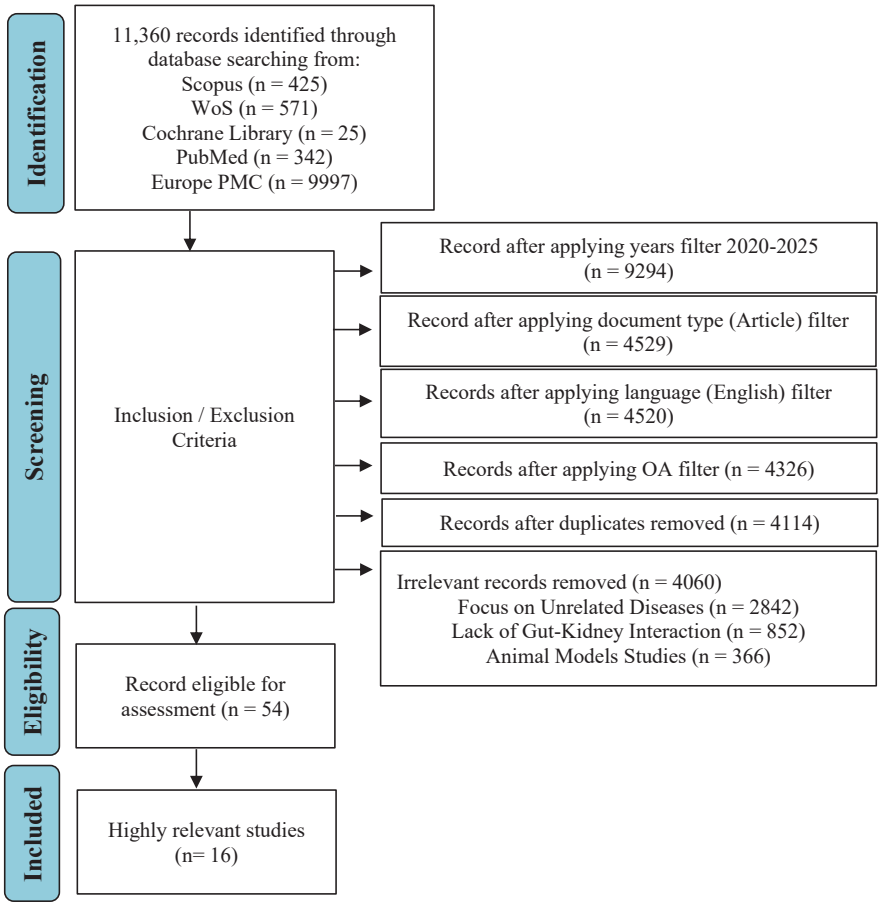

Figure 1. PRISMA flow diagram.

Table 1. Risk of bias assessment summary of RCTs

Author(s) and Year	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Arteaga-Muller et al 2024 (40)	Low	Low	Low	Low	Low	Low	Low
Jiang et al 2023 (38)	Low	Low	Low	Low	Low	Low	Low
Lydia et al 2022 (41)	Low	Low	Low	Low	Low	Low	Low
Mauri et al 2022 (33)	Low	Low	Low	Low	Low	Low	Low
Sohn et al 2022 (39)	Low	Low	Low	Low	Low	Low	Low

Table 2. Newcastle-Ottawa Quality (NOS) assessment scale

Author(s) & Year	Selection	Comparability	Outcome	NOS Score
Peters et al, 2023 (26)	****	**	***	8/9
Balint et al, 2023 (27)	****	**	***	8/9
Zheng et al, 2024 (28)	****	**	***	8/9
Wang et al, 2023 (29)	***	**	***	7/9
Yan et al, 2024 (30)	***	**	***	7/9
Balint et al, 2023 (31)	****	**	***	8/9
Lu et al, 2023 (32)	***	**	***	7/9
Chen et al, 2021 (34)	****	**	***	8/9
Lao et al, 2023 (35)	****	**	****	9/9
Wang et al, 2024 (36)	***	**	***	7/9
Huang et al, 2024 (37)	***	**	***	7/9

Note: * = 1 point on the NOS. Max scores: Selection = 4, Comparability = 2, Outcome = 3. Higher stars indicate better quality.

Table 3. Study characteristics

Author(s) & Year	Study design	Sample size	Population	Duration
Peters et al 2023 (26)	Cross-sectional	2438	Hispanic/Latino adults	6 years
Balint et al 2023 (27)	Cross-sectional	90	T2DM patients	10 months
Zheng et al 2024 (28)	Cross-sectional	20380	US adults	10 years
Wang et al 2023 (29)	Cross-sectional	68	Patients with CKD	-
Yan et al 2024 (30)	Cross-sectional	18340	T2DM and DN	-
Balint et al 2023 (31)	Cross-sectional	90	T2DMs	-
Lu et al 2023 (32)	Cross-sectional	115	DN patients	1 years
Mauri et al 2022 (33)	RCT	60	Advanced CKD	2 to 3 months
Chen et al 2021 (34)	Observational	100	Healthy, Diabetes, DN	
Lao et al 2023 (35)	Prospective	28	Overweight and obese	12 weeks
Wang et al 2024 (36)	Cross-sectional	3836	US adults with T2DM	19 years
Huang et al 2024 (37)	Cross-sectional	160	-	46.34 months
Jiang et al 2023 (38)	RCT	31	T2DM	12 weeks
Sohn et al 2022 (39)	RCT	81	Korean	12 weeks
Arteaga-Muller et al 2024 (40)	RCT	28	Patients with CKD	6 months
Lydia et al 2022 (41)	RCT	60	CKD patients	-

Abbreviations: T2DM: Type 2 diabetes mellitus; DN: Diabetic nephropathy; CKD: Chronic kidney disease; RCT: Randomized controlled trial.

Other markers such as sArg, sIS and uBCA also correlate highly with the progression of nephropathy, eGFR, and serum creatinine levels. Probiotic therapy and other approaches such as TRF have effectively stabilized eGFR and decreased kidney injury. However, some studies indicate no significant change in nephropathy or serum creatinine. The evidence indicates that gut microbiome constituents and metabolites are significant factors in developing nephropathy. They have predictive value for kidney function at many stages of kidney disease.

Table 6 illustrates significant relations among microbiota, metabolic syndrome, and some biomarkers. Certain microbial taxa, such as indolepropionate and beta-cryptoxanthin, are associated with diabetes and metabolic health. Meanwhile, sArg (serum arginine), sIS (serum indoxyl sulfate), and sBCA (serum butenoylcarnitine) metabolite changes are associated with endothelial and renal dysfunctions and metabolic syndrome. In addition, intake of probiotics was shown to lower urinary oxalate and uremic toxin excretion, enhancing some metabolic parameters. Markers of inflammation, as well as insulin sensitivity and lipid metabolism, have been influenced by probiotic supplementation and the TRF dietary approach. Metabolic disturbances are also associated with the trimethylamine N-oxide (TMAO) metabolite, which is known to be related to cardiovascular and kidney diseases. Generally, gut dysbiosis and high levels of uremic toxins can be improved by FMT interventions.

Discussion

The studies included in the current systematic review differ remarkably in their design, sample size, and study duration. Most of the studies are cross-sectional with sample sizes varying from 90 to 20,380 and study durations ranging from 6 months to 19 years. Some studies are more specific and examine Hispanic/Latino adults, patients with T2DM, and patients with advanced CKD or diabetic nephropathy. Moreover, RCTs and other observational studies have assessed the effects of gut microbiota on renal function and the progression of nephropathy over 12 weeks to 6 months. Various studies have illustrated the link between the changes in the gut microbiota composition and the emergence of diabetic kidney disease. This causes the reduction of beneficial bacteria such as *Faecalibacterium*, and the rise of pathogenic bacteria, such as *Proteobacteria* and *Clostridium*. One study noted that *Hungatella* and *Escherichia genus* were raised in DKD (diabetic kidney disease), while butyrate-producing bacteria were lowered, indicating that these specific microbiome alterations are some of the contributors towards the development of DKD (42). However, even though evidence exists to support the role of gut microbiota in nephropathy, the differences in study design as well as sample size provide problems in accuracy and results reliability (43). Multiple systematic reviews and meta-analyses have confirmed that CKD patients exhibit gut dysbiosis with decreased microbial diversity and specific compositional changes. For instance, *Roseburia* and *Faecalibacterium*, both beneficial, short-chain fatty acid-producing genera, are consistently reduced in CKD and DKD patients, while potentially harmful taxa like Proteobacteria (including *Escherichia* and *Streptococcus*) are enriched (44). These changes correlate with disease severity and renal function decline. Although most studies

Table 4. Microbial taxa, microbiota changes and impact on renal function

Author(s) and Year	Microbial taxa	Microbiota changes	Key findings and impact on renal function
Peters et al 2023 (26)	*Prevotella, Faecalibacterium, Roseburia,* Clostridia, others	Reduced diversity in low eGFR participants	Higher eGFR linked to beneficial microbiome. Microbiome changes associated with kidney function decline.
Balint et al 2023 (27)	sArg, sBCA, sSorb, sIS, uIS, uPCS	Decreased sArg, increased sIS, sBCA, and sSorb	Metabolite changes (sArg, sIS, sBCA, sSorb) differentiate DKD subgroups.
Zheng et al 2024 (28)	*Oxalobacter, Lactobacillus, Bifidobacterium*	↓ *Oxalobacter* in KSD patients	Higher live microbe intake lowers KSD risk.
Wang et al 2023 (29)	Proteobacteria, *Lactobacillaceae*, *Ruminococcus*	Decreased SCFA-producers, increased pathogens	Dysbiosis and metabolites linked to CKD severity.
Yan et al 2024 (30)	Pro, *Lactobacillaceae*, Veillonellaceae	Increased Pro, decreased *Lactobacillaceae*	Increased Pro, decreased *Lactobacillaceae* and Veillonellaceae in ESRD.
Balint et al 2023 (31)	-	Metabolite levels reflect gut microbiota activity	Biomarkers like arginine, indoxyl sulfate are linked to DKD.
Lu et al 2023 (32)	Clostridium-XVIII, *Gemmiger*, *Flavonifractor*, *Eisenbergiella*	Decrease in Clostridium-XVIII and *Gemmiger*	Microbiota differences between DN, DM, and controls linked to DN progression.
Mauri et al 2022 (33)	*Bifidobacterium longum*, *Lactobacillus reuteri*	Decreased uremic toxins	Probiotics reduce uremic toxins, delay ESRD progression, no eGFR improvement.
Chen et al 2021 (34)	*Alistipes, Bacteroides, Ruminococcus*	Reduced diversity in Stage III DN	Gut microbiota diversity decreases with DN progression, negatively correlates with eGFR.
Lao et al 2023 (35)	Akkermansia, Lachnospiraceae, Clostridiales, Verrucomicrobia	Beneficial gut shifts in TRF group	TRF group improved eGFR, reduced uric acid and weight loss.
Wang et al 2024 (36)	*Lactobacillus, Bifidobacterium*	Increased diversity in high intake group	High microbe intake linked to lower DKD prevalence and creatinine.
Huang et al 2024 (37)	TMA-producing gut microbiome	TMAO levels correlate with kidney biomarkers	TMAO levels linked to arterial stiffness in PD patients.
Jiang et al 2023 (38)	Bacteroidaceae-Bacteroides, Prevotellaceae	Increased probiotics, decreased diversity	SL formula reduced glucose, BMI, insulin resistance, CRP.
Sohn et al 2022 (39)	*Lactobacillus plantarum, Enterococcus hirae*	↑ *L. plantarum,* ↓ *Actinobacteria*	LPK reduced cholesterol and triglycerides.
Arteaga-Muller et al 2024 (40)	Firmicutes, Bacteroidetes, Proteobacteria, *Roseburia* spp.	Decrease in Firmicutes, increase in Bacteroidetes	FMT group had less CKD progression, stable renal function.
Lydia et al 2022 (41)	*Lactobacillus acidophilus, Bifidobacterium longum*	Increased saccharolytic bacteria	Synbiotics improved constipation, but no effect on indoxyl sulfate.

Abbreviations: eGFR, Estimated glomerular filtration rate; sArg, Serum arginine; sBCA, Serum branched-chain amino acids; sSorb, Serum sorbitol; sIS, Serum indoxyl sulfate; uIS, Urinary indoxyl sulfate; uPCS, Urinary p-cresyl sulfate; DKD, Diabetic kidney disease; KSD, Kidney stone disease; SCFA, Short-chain fatty acids; CKD, Chronic kidney disease; ESRD, End-stage renal disease; DN, Diabetic nephropathy; DM, Diabetes mellitus; TRF, Time-restricted feeding; TMA, Trimethylamine; TMAO, Trimethylamine N-oxide; PD, Peritoneal dialysis; BMI, Body mass index; CRP, C-reactive protein; FMT, Fecal microbiota transplantation; Pro, Proteobacteria.

are cross-sectional or observational, some RCTs have begun to assess the impact of probiotics, prebiotics, and synbiotics on gut microbiota modulation and renal outcomes. These interventions show promise in restoring beneficial bacteria and mitigating inflammation and gut permeability, potentially slowing CKD progression, but larger, longer-term trials are needed to confirm efficacy (45,46). All of the studies in this systematic review show a common finding which is the reduced microbiome diversity amongst participants with low estimated glomerular filtration rate and CKD. Taxa that associate with good kidney functions such as *Prevotella* and *Faecalibacterium* alongside *Oxalobacter* are associated, while taxa seen with CKD, Proteobacteria and *Clostridium*, are also seen. Moreover, some markers such as indoxyl sulfate and arginine have strong associations with nephropathy. In fact, it appears as if this reduced diversity in the microbiome, especially in patients with CKD worsens the condition even more. Another similar study reported that subjects suffering from CKD and low eGFR

Table 5. Nephropathy associations and correlations with eGFR and serum creatinine

Author(s) and Year	Change in nephropathy	Association with nephropathy	Correlation with eGFR and creatinine
Peters et al 2023 (26)	Microbiome-related metabolites (p-cresol glucuronide, imidazole propionate) linked to nephropathy.	Microbiome features associated with kidney health, eGFR and UAC ratio.	Significant correlation between microbiome and eGFR, higher eGFR linked to beneficial species.
Balint et al 2023 (27)	Decreased sArg and increased metabolites linked to nephropathy progression.	Strong correlation of metabolites with nephropathy progression.	Significant association with biomarkers (sArg, sIS, uBCA, uIS) and eGFR. Strong correlation between biomarkers (podocalyxin, KIM-1) and serum creatinine.
Zheng et al 2024 (28)	-	KSD linked to altered microbiota.	-
Wang et al 2023 (29)	CKD severity linked to dysbiosis and altered metabolism.	Gut microbiota disturbances linked to CKD progression.	Negative correlation with pathogenic taxa, positive with protective taxa (Lactobacillaceae). Positive correlation with serum creatinine and metabolites.
Yan et al 2024 (30)	Altered kidney function and albuminuria across stages.	Lactobacillaceae linked to better kidney health.	Lactobacillaceae and Veillonellaceae positively correlate with eGFR.
Balint et al 2023 (31)	Biomarkers for different DKD stages, correlating with nephropathy progression.	Significant differences in metabolites across DKD stages.	Correlations with biomarkers like arginine, but no detailed eGFR data.
Lu et al 2023 (32)	Microbiota linked to diabetic nephropathy severity.	Strong association between microbiota and nephropathy severity.	Negative correlation with Clostridium-XVIII, positive with Flavonifractor, Eisenbergiella. Correlated with renal markers (eGFR, UACR).
Mauri et al 2022 (33)	Delayed ESRD progression and dialysis initiation in probiotics group.	Probiotics group showed better management of proteinuria and delayed dialysis.	No significant correlation with eGFR, but more stable eGFR levels in probiotics group. No significant change in creatinine.
Chen et al 2021 (34)	Higher detrimental gut bacteria prevalence in DN patients.	Higher presence of Bacteroides and Lachnoclostridium in DN.	Negative correlation with Ruminococcus torques. Increased serum creatinine.
Lao et al 2023 (35)	Decreased creatinine and uric acid, suggesting nephroprotective effects.	TRF group had improved renal parameters, supporting nephroprotective effects.	TRF group improved eGFR (+3.1 ml/min/1.73m²). TRF group showed reduced creatinine levels.
Wang et al 2024 (36)	High live microbe intake linked to lower DKD risk.	Inverse association between high live microbe intake and DKD.	Lower creatinine in high live microbe group.
Huang et al 2024 (37)	No specific change in nephropathy, but arterial stiffness observed.	TMAO levels associated with arterial stiffness in PD patients.	TMAO inversely correlated with eGFR. TMAO associated with renal function decline.
Jiang et al 2023 (38)	Glucose metabolism and inflammation improvements suggest nephroprotective effects.	Gut microbiota modulation may improve kidney health.	Not available
Arteaga-Muller et al 2024 (40)	FMT group had less CKD progression (13.3%) vs. placebo (53.8%).	Less CKD progression in FMT group, potential nephroprotective effect.	Improvement in eGFR in the FMT group. No significant creatinine difference.
Lydia et al 2022 (41)	No significant nephropathy change, but improved gastrointestinal symptoms.	Synbiotics had no significant effect on nephropathy progression.	Not available

Abbreviations: eGFR, Estimated glomerular filtration rate; UACR, Urinary albumin-to-creatinine ratio; sArg, Serum arginine; sIS, Serum indoxyl sulfate; uBCA, Urinary branched-chain amino acids; uIS, Urinary indoxyl sulfate; DKD, Diabetic kidney disease; KSD, Kidney stone disease; CKD, Chronic kidney disease; ESRD, End-stage renal disease; DN, Diabetic nephropathy; TRF, Time-restricted feeding; TMAO, Trimethylamine N-oxide; PD, Peritoneal dialysis; FMT, Fecal microbiota transplantation; KIM-1, Kidney injury molecule-1; CRP, C-reactive protein.

do have reduced microbiome diversity which is, in contrast, healthier individuals. Also, it was reported that this diversity reduction is associated with health complications and increased CKD progression (47). The contribution of the gut microbiota to the production and metabolism of uremic toxins is no less important. Alterations in gut microbiota during CKD cause changes in intestinal flora which promote the synthesis of these toxins, which further drives kidney damage (48). The disappearance of beneficial taxa such as *Faecalibacterium* is known to be associated with compromised kidney function, while harmful taxa are known to worsen CKD. These studies support the need for balanced gut microbiota that would avoid the build-up of toxins and enhance metabolic activities that are beneficial (49). A 2023 systematic review analyzing 69 studies found significantly decreased microbial diversity and specific depletion of beneficial genera such as *Roseburia* and *Ruminococcus* in CKD patients, especially those with end-stage kidney disease (50). A consistent observation across studies is the reduced gut microbial diversity in CKD patients compared to healthy controls. This reduction in diversity correlates

Table 6. Associations of microbiota, metabolic syndrome, and biomarkers

Author(s) and Year	Marker	Role in metabolic syndrome	Increased/Decreased
Peters et al 2023 (26)	Indolepropionate, beta-cryptoxanthin, p-cresol glucuronide, imidazole propionate	Linked to metabolic health and diabetes.	Increased: indolepropionate, beta-cryptoxanthin. Decreased: p-cresol glucuronide, imidazole propionate.
Balint et al 2023 (27)	sArg, sIS, sBCA, sSorb	Implicated in endothelial and renal dysfunction, metabolic syndrome.	Decreased: sArg. Increased: sIS, sBCA, sSorb.
Zheng et al 2024 (28)	Urinary oxalate, serum creatinine	Linked to diabetes and hypertension.	Decreased: urinary oxalate with probiotic intake.
Wang et al 2023 (29)	Fecal hydroquinone, *Ruminococcus bromii*, L-cystine, 12-keto-tetrahydro-LTB4	Dysbiosis linked to CKD severity and metabolic dysfunction.	Increased: Hydroquinone, L-cystine. Decreased: SCFA-producing bacteria.
Yan et al 2024 (30)	UACR, eGFR, microbiome markers	T2DM and DN influence microbiome and kidney function.	-
Balint et al 2023 (31)	Arginine, ADMA, hippuric acid, indoxyl sulfate, p-cresyl sulfate, L-acetylcarnitine, butenoylcarnitine, sorbitol.	Metabolites linked to DKD and metabolic processes.	Decreased: Arginine, Hippuric acid. Increased: ADMA, Indoxyl sulfate, Butenoylcarnitine.
Lu et al 2023 (32)	Clostridium-XVIII, *Gemmiger*, Flavonifractor, Eisenbergiella	Alterations in microbiota linked to T2DM and nephropathy.	Increased: Flavonifractor, Eisenbergiella. Decreased: Clostridium-XVIII, *Gemmiger*.
Mauri et al 2022 (33)	Lp-PLA2, Indoxyl-sulphate, P-cresyl sulphate	Probiotics reduce toxins, improve lipid profiles.	Decreased: Lp-PLA2, IS. Increased: cholesterol, LDL.
Chen et al 2021 (34)	24-h Urinary protein, cholesterol	Linked to metabolic changes and inflammation.	Increased: *Alistipes, Bacteroides.*
Lao et al 2023 (35)	Uric acid, total protein, TNF-α, IL-6	TRF improved weight loss, insulin sensitivity.	Decreased: Uric acid, TNF-α. Increased: Total protein, IL-6.
Wang et al. 2024 (36)	HbA1c, serum creatinine, eGFR, UACR	Improved metabolic markers (lower HbA1c, serum creatinine).	Lower: HbA1c, serum creatinine.
Huang et al 2024 (37)	Serum trimethylamine N-oxide (TMAO)	TMAO linked to metabolic disturbances in kidney and cardiovascular disease.	Increased: TMAO in arterial stiffness.
Jiang et al 2023 (38)	HbA1C, FPG, PBG, FIL, CRP	Reduces insulin resistance, postprandial glucose, inflammation.	Decreased: CRP, insulin resistance. Increased: Ruminiclostridium9.
Sohn et al 2022 (39)	Total cholesterol, triglycerides	Improved lipid profile, beneficial for obesity.	Decreased: Total cholesterol, triglycerides.
Arteaga-Muller et al 2024 (40)	Roseburia spp., SCFAs, uremic toxins	FMT improved gut dysbiosis, decreased uremic toxins.	Decreased: *Roseburia* spp., Uremic toxins. Increased: SCFAs.
Lydia et al 2022 (41)	Indoxyl Sulfate, PAC-SYM, PAC-QOL questionnaires	Improved gastrointestinal symptoms, no reduction in indoxyl sulfate.	Increased improvement in quality of life and constipation symptoms.

Abbreviations: ADMA, Asymmetric dimethylarginine; CRP, C-reactive protein; DKD, Diabetic kidney disease; DN, Diabetic nephropathy; eGFR, Estimated glomerular filtration rate; FMT, Fecal microbiota transplantation; FPG, Fasting plasma glucose; HbA1c, Glycated hemoglobin; IL-6, Interleukin-6; IS, Indoxyl sulfate; KSD, Kidney stone disease; LDL, Low-density lipoprotein; Lp-PLA2, Lipoprotein-associated phospholipase A2; PAC-QOL, Patient assessment of constipation-quality of life; PAC-SYM, Patient assessment of constipation symptoms; PBG, Postprandial blood glucose; sArg, Serum arginine; sBCA, Serum branched-chain amino acids; SCFA, Short-chain fatty acids; sIS, Serum indoxyl sulfate; sSorb, Serum sorbitol; T2DM, Type 2 diabetes mellitus; TNF-α, Tumor necrosis factor alpha; TRF, Time-restricted feeding; TMAO, Trimethylamine N-oxide; UACR, Urinary albumin-to-creatinine ratio; uIS, Urinary indoxyl sulfate.

with lower estimated glomerular filtration rate, indicating worsening kidney function (51,52). Network meta-analyses from 2025 indicate that interventions with probiotics, prebiotics, and synbiotics can reduce these uremic toxins, suggesting a therapeutic avenue targeting gut microbiota modulation (53). Moreover, altered microbiota compositions have been linked to mortality risk in ESKD patients, highlighting clinical relevance (54). Current systematic review presents the likelihood of effectiveness of various interventions such as probiotics, time restricted feeding, and other dietary approaches on the composition of gut microbiota. These approaches assist in the reduction of uremic toxins, hence delaying the progression of end stage renal disease. One study pointed out that modulation of gut microbiota diversity and composition is likely to enhance the overall outcomes in diabetic nephropathy (55). Additionally, dietary and lifestyle changes are known to improve gut microbiome composition, especially in patients with CKD (56). Besides dietary guidelines and probiotics, fecal microbiota transposition is evolving as a promising therapeutic approach to enhance metabolic profiles, increase insulin sensitivity, and modulate inflammation. Certain microbial taxa, including *Lactobacillaceae* and *Veillonellaceae*, have been linked to improved kidney health, whereas the pathogenic Proteobacteria is correlated with the CKD progression. The microbiome-related metabolites p-cresol glucuronide and imidazole propionate are also showing their strong associations with nephropathy (57). Multiple systematic reviews and meta-analyses demonstrate that supplementation with probiotics, prebiotics, and synbiotics significantly reduces circulating levels of key uremic toxins, notably p-cresyl sulfate and indoxyl sulfate (58). Additionally, these interventions reduce inflammatory markers, such as CRP and IL-6, and oxidative stress in hemodialysis and ESRD patients (59). Time-restricted feeding, a form of intermittent fasting, has been shown to beneficially alter the gut microbiota composition, increasing the abundance of taxa associated with metabolic health (e.g., *Akkermansia*, *Ruminococcaceae*, *Lachnospiraceae*). While direct evidence in ESRD is emerging, the modulation of gut flora by TRF could theoretically reduce the generation of gut-derived uremic toxins, supporting renal health (60). The findings of other studies also suggest that modulating the gut microbiota through these interventions can effectively reduce specific uremic toxins. However, further trials are necessary to better understand microbiota modulation and its impact on intestinal bacterial composition (61). Current systematic review findings portray that the gut microbiota has an essential role in metabolic syndrome and associated biomarkers. Various products such as sArg, sIS, and sBCA perform Endothelial and renal dysfunction which causes metabolic disorders. These probiotic interventions have been effective in lowering urinary oxalate excretion and the levels of uremic toxins, apparently leading to better metabolic profiles. Some literature reveals that the gut microbiota might help mitigate some of the metabolic derangements seen in CKD and diabetes due to its effect on metabolic homeostasis (62). Moreover, the industry has also widely covered her role with microbiota in systemic inflammation. Some inflammatory biomarkers have been suggested such as C-reactive protein, interleukin-6, and lipopolysaccharides and these assist to mediate the maintenance of the intestinal barrier and promote chronic inflammation (63). Likewise, some specific metabolites such as hippuric acid and indole-3-acetic acid have been shown to enhance the progression of diabetic kidney disease, thus adding further evidence on the association of the microbiome and disease mechanisms (64). In conclusion, this study underscores the critical role of gut microbiota in metabolic diseases and emphasizes the potential for microbiome-based interventions to improve metabolic and renal health outcomes. Gut microbiota-derived metabolites such as bile acids, short-chain fatty acids, trimethylamine N-oxide, and tryptophan metabolites have been implicated in the onset and progression of metabolic disorders like non-alcoholic fatty liver disease, a condition closely related to MetS. These metabolites influence immune regulation and metabolic pathways, contributing to disease pathogenesis (65). Several studies have confirmed that gut microbiota composition and diversity are significantly altered in MetS patients. For instance, a 2020 study profiling treated MetS patients revealed that gut microbiota diversity varies among individuals but can be grouped into enterotypes associated with specific metabolic parameters and inflammatory markers like IL-1β and IL-18, which are linked to metabolic dysfunction (66). Another study found that patients with MetS, accompanied by elevated gamma-glutamyl transpeptidase, a marker of liver dysfunction, showed reduced gut microbial richness and significant compositional differences compared to those with normal GGT (gamma-glutamyl transferase), indicating a connection between gut dysbiosis and metabolic complications (67). Meta-analyses from 2025 indicate that probiotic, prebiotic, and synbiotic interventions can modulate gut microbiota, significantly reducing body mass index (BMI) and waist circumference in MetS patients. However, effects on other anthropometric indices are less clear (68). These microbial therapies likely improve metabolic profiles by reducing uremic toxins and urinary oxalate, which are linked to endothelial and renal dysfunction, key contributors to metabolic disorders.

Limitations of the study

This systematic literature review faces a number of shortcomings. The selected studies differ in their methods, sample sizes, and characteristics of the study population.

This could result in bias and reduce the generalizability of the findings. Differences in the microbiome analyses, such as the use of 16S rRNA sequencing in comparison to metagenomic sequencing, make direct study comparisons even more challenging. Also, the fact that most studies are cross-sectional or observational poses a challenge in terms of measuring the causative relationship between gut microbiota and the progression of nephropathy. The absence of standardized frameworks for microbiome-based interventions, such as probiotics and dietary changes, also reduces the consistency of the aforementioned outcomes. Lastly, confounders such as the use of medications, other lifestyle factors, and genetic predisposition have not been adequately addressed in many studies, warranting the need for more comprehensive, multicenter, and longitudinal studies to validate these results.

Conclusion

This systematic review sheds light on the important contribution of gut microbiota to developing of nephropathy in patients diagnosed with metabolic syndrome. The studies involving different designs, sample sizes, and durations consistently demonstrated that changes in gut microbiota are closely linked to the deterioration of kidney function, the advancement of nephropathy, and the exacerbation of metabolic disorders. Such findings emphasize the critical role of gut health in the pathophysiology of kidney disease, highlighting its potential as a key factor in disease progression. Numerous studies share the theme of decreased microbial diversity among patients suffering from CKD and diabetic nephropathy. Researchers found that beneficial microbial taxa, such as *Prevotella*, *Faecalibacterium*, and *Oxalobacter*, contribute to improved kidney function, while pathogenic taxa, including Proteobacteria and Clostridium, exacerbate CKD. The imbalance between these microbial communities, often referred to as dysbiosis, may lead to inflammation, metabolic disturbances, and progressive kidney injury. Furthermore, microbiome-derived metabolites like indoxyl sulfate, p-cresol glucuronide, and imidazole propionate are strongly associated with nephropathy markers, such as glomerular filtration rate and serum creatinine levels, which are commonly used to assess kidney function. While some studies noted no significant changes in the progression of nephropathy, they did observe substantial improvements in estimated glomerular filtration rate and other metabolic markers. This suggests that although gut microbiota may not directly reverse disease progression in all cases, interventions such as probiotics, FMT, and dietary changes, such as TRF, may provide significant benefits. These strategies have been shown to alter gut microbiota composition, minimize uremic toxin production, and preserve kidney function, further supporting the potential of microbiome-based therapies. These findings underscore the strong and persistent need to evaluate the effectiveness of microbiome interventions in clinical settings. This growing body of evidence highlights the relationship between gut microbiota, nephropathy, and metabolic syndrome, suggesting that gut microbial composition and its metabolites could be promising therapeutic targets and biomarkers for predicting kidney disease progression. However, more robust longitudinal and interventional studies are required for these associations to be fully validated and for microbiome-based nephropathy therapeutics to be developed. Such studies will be crucial to establish causality and explore microbiota modulation's therapeutic potential in managing kidney diseases.

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Conflicts of interest

There are no competing interests.

Consent for publication

This study does not include any individual person's data in any form (including individual details, images, or videos). As the review is based solely on secondary data extracted from publicly available scientific literature, informed consent for publication was not required.

Data availability statement

This systematic review is based entirely on previously published studies that are openly accessible through academic databases including Scopus, Web of Science, PubMed, Cochrane Library, and Europe PMC. All data supporting the findings of this study are included in the article and its references. No new primary data were generated or analysed by the authors. Further information is available from the corresponding author upon reasonable request.

Ethical issues

This systematic review is based exclusively on

previously published studies and does not involve direct interaction with patients. Therefore, the primary ethical considerations relate to the appropriate handling, analysis, and interpretation of data obtained from the included literature. The review was conducted in full compliance with the PRISMA checklist, and the protocol was registered on the PROSPERO website (ID: CRD420251053100). Furthermore, all relevant ethical standards have been fully observed by the authors, including the avoidance of plagiarism, data fabrication, and duplicate publication.

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