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NEPHROLOGY - REVIEW

The gut microbiota and its relationship with chronic kidney disease

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Abstract
Chronic kidney disease (CKD) is a worldwide health problem, because it is one of the most common complications of metabolic diseases including obesity and type 2 diabetes. Patients with CKD also develop other comorbidities, such as hypertension, hyperlipidemias, liver and cardiovascular diseases, gastrointestinal problems, and cognitive deterioration, which worsens their health. Therapy includes reducing comorbidities or using replacement therapy, such as peritoneal dialysis, hemodialysis, and organ transplant. Health care systems are searching for alternative treatments for CKD patients to mitigate or retard their progression. One new topic is the study of uremic toxins (UT), which are excessively produced during CKD as products of food metabolism or as a result of the loss of renal function that have a negative impact on the kidneys and other organs. High urea concentrations significantly modify the microbiota in the gut also, cause a decrease in bacterial strains that produce anti-inflammatory and fuel molecules and an increase in bacterial strains that can metabolize urea, but also produce UT, including indoxyl sulfate and p-cresol sulfate. UT activates several cellular processes that induce oxidative environments, inflammation, proliferation, fibrosis development, and apoptosis; these processes mainly occur in the gut, heart, and kidney. The study of the microbiota during CKD allowed for the implementation of therapy schemes to try to reduce the circulating concentrations of UT and reduce the damage. The objective of this review is to show an overview to know the main UT produced in end-stage renal disease patients, and how prebiotics and probiotics intervention acts as a helpful tool in CKD treatment.

Keywords Chronic kidney disease · Microbiota · Dysbiosis · Probiotics · Prebiotics

Chronic kidney disease (CKD)

Table 1 shows all abbreviation used in this report. CKD has been increasing in the last decade, and it is considered an economic problem in health systems around the world due to its higher treatment costs. Because CKD has no visible symptoms and is difficult to recognize, CKD is known as a silent disease that is diagnosed late and often has a poor outcome. CKD is characterized by a gradual loss of kidney function and irreversible changes in the renal structure; its progression causes cardiovascular complications and finally death.

Causes of CKD include type 2 diabetes mellitus progression, hypertension, metabolic syndrome, glomerulonephritis, IgA glomerulonephritis, and autoimmune diseases. CKD is clinically defined as a sustained loss of renal function, determined as a fall in glomerular filtration rate (GFR) < 60 ml/min or the presence of albuminuria for 3 or more months [1–5].

Clinical studies suggest that CKD is associated with other comorbidities that increase the risk of developing cardiovascular diseases or death, such as acute kidney injury, hyperlipidemias, hyperglycemia, smoking, obesity, cardiovascular disease, nephrotoxic drugs, and hypertension [6]. Therefore, adjustments in lifestyle such as reducing body mass index, smoking, and salt consumption are critical to avoid CKD progression [2]. In addition, it is highly recommended to include 30 min of daily exercise and to change dietary habits, as many studies show that the gut microbiota was altered in those

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Table 1 List of abbreviations used

Symbol	interpretation	Symbol	interpretation
CKD	Chronic kidney disease	IL-6	Interleukin 6
UT	Uremic toxins	BUN	Blood nitrogen urea
ESRD	End-stage renal disease	MCP-1	Monocyte chemoattractant protein 1
GFR	Glomerular filtration rate	HD	Hemodialysis
IS	Indoxyl sulfate	HAM-RS2	Amylose resistant starch
PCS	p-Cresyl sulfate	RCT	Randomized controlled trial
PC	p-Cresyl	TNF-α	Tumor necrosis factor alpha
TMAO	Trimethylamine *N*-oxide	AST-120	Charcoal activated pellets
IAA	Indole acetic acid	AG	Acacia gum
PCG	p-Cresyl glucuronide	CFU	Colony forming units
SCFAs	Short-chain fatty acids	CPR	C reactive protein
OA	Oxalic acid	VCAM	Vascular cell adhesion molecule 1
ROS	Free radical oxygen spices	ICAM	Intercellular adhesion molecule 1
CRP	C reactive protein	TLR	Toll like receptors
NFkB	Nuclear factor kappa B	HA	Hippuric acid
OUT	Operational taxonomic unit	FTI	Fibrosis tubule interstitial
SCr	Serum creatinine	CCr	Creatinine clearance
α-sma	Smooth muscle actin	PAI-1	Plasminogen activator inhibitor 1
Pi	Inorganic phosphorus	MAP	Mean arterial pressure

patients. Moreover, the presence of UT is considered a marker of CKD due to higher levels observed in the plasma of stage III–V CKD patients, see Table 2. Recently, the microbiota and UT have been the focus of relevant and novel research [7].

The microbiota

Microbiota is defined as the coexistence of all microorganisms living in the host, which consists mainly of bacteria, but also includes viruses, archaea, fungi, and unicellular eukaryotes [7–9].

In the last decade, the microbiota has been recognized as an essential part of human health. Having healthy gut flora (microbiota) is associated with good health [10]. It has been estimated that the human body has at least 35,000 different species of microorganisms and has a population of 10×10^{14} bacteria. In normal conditions, the intestinal microbiota is mainly composed of five phyla; significant proportions in the colon are *Firmicutes* and *Bacteriodetes*, followed by *Actinobacteria*, *Verrucomicrobia,* and, in a lower proportion, *Proteobacteria* [10].

The components and functions of microbiota

The microbiota is responsible for metabolizing diet components and improving digestion by expressing several enzymes absent in the human genome, including proteases, galactosidases, hexosaminidases, and tryptophanase, among others. The primary function of these bacteria is to metabolize the carbohydrates and oligosaccharides from the diet; these components are their energy sources and are necessary for the beginning of the fermentation process. Some *Firmicutes* can synthesize biotin, riboflavin, ascorbic acid, and other molecules. One of the most critical roles of microbiota is to participate in the biosynthesis of short-chain free fatty acids (SCFAs), such as butyrate, propionate, and acetate, which are fuel sources for the host. These SCFAs are involved in anti-inflammatory or antiproliferative processes. Other phyla, such as *Prevotella* and *Rumminococus*, participate in folate synthesis, vitamin K, and vitamin B12 production [7, 10, 11].

The microbiota is also involved in protection against pathogens and xenobiotics. It participates directly in antibiotic resistance roles, anti-inflammatory states, intestinal proliferation, maintaining energy sources and pH regulation; it was also recently shown to be involved in the immune response. In the last two decades, changes in the ratio of *Firmicutes*/*Bacteriodetes* were shown to be directly related to inflammatory bowel disease, irritant bowel disease, and dysbiosis. The microbiota contributes to the progression of many other pathologies outside of the intestine, including Alzheimer's disease, neurological disorders, metabolic disorders, such as diabetes, obesity and metabolic syndrome, and the development of hypertension [12–18].

Therefore, there are currently reported therapies and efforts directed toward maintaining the intestinal flora in balance using prebiotics and probiotics, and they have been shown to be effective against several pathologies. However,

Table 2 Identification of uremic toxins in patients during CKD

Study and stage CKD	Kidney markers	Uremic toxins	Main remarks
CKD patients $n=50$ HD and peritoneal dialysis [32]	**SCr** **BUN**	**IS** **PCS** **TNF** **CD4$^+$** **CD28$^+$**	Incubation with IS and PCS induces pro-inflammatory markers in human monocytes. Inducing immune response dysfunction by increasing apoptosis in endothelial cells leads to CVD
CKD patients $n=21$ Stage III–IV HD patients (54 months) [31]	**BUN** **SCr** **IL-6** **MCP-1**	**IS** **PCS** **IAA**	Uremic toxins contributed to the inflammatory state in CKD
ESRD patients $n=7$ HD. Measurements before and after dialysis [37]	**BUN** **SCr**	**TMAO predialysis** **TMAO clearance** **BUN-clearance**	TMAO has elevated values in CKD patients. The clearance of BUN and TMAO could be useful as CKD markers
Percutaneous coronary intervention patients with or without CKD $n=403$ [52]	GFR	**PCS** **Left ventricular infraction**	PCS reduces left ventricular ejection fraction in patients with or without CKD High concentrations of PCS and the presence of CKD increase the risk to impaired left ventricular infractions
CKD patients with GFR <60 ml/min $n=232$ Non-dialysis [50]	GFR	**PCS** **IS**	CKD patients with lower GFR have proportionally higher plasma levels of PCS and IS High IS levels are associated with cognitive impairment in stage III CKD
CKD patients stage II–V With or without dialysis [90]	GFR	**PCS** **PCG** **HA** **IAA** **IS**	The protein binding percentage and free uremic toxins increased according to degree of kidney injury. Stage V had the highest binding percentage
CKD patients in stage III–IV $n=10$ GFR 10–34 ml/min [91]	**SCr** **BUN**	**Hippuric acid** **PCS** **TMAO** **Dimethyl sulfone** **2-Hydroxyisobutyric acid**	CKD increases the uremic toxic substances. The isolation of 14 helps to identify new molecules such as DMSO2 and 2HIBA implicated in CKD progression
Human proximal tubular HK-2 cells Incubated with IS and IAA [92]		**ROS** **PAI-1**	IS and IAA induce ROS production and expression of PAI-1, activating NFkB Leading to a pro-inflammatory state that could contribute to kidney damage

Bold indicates a significant increase of these parameters. Underlined characters indicate a significant decrease of these parameters

it is difficult to know the precise phyla that were modified in each patient.

Prebiotics and probiotics

Prebiotics are defined as "molecules or substrates that are selectively used by host gut microbiota, and they have a positive effect" [12]. Originally, prebiotics were complex carbohydrates, oligosaccharides, fructans, galactans, and starch. In recent years, polyphenols have been used as prebiotics, because their metabolism occurs in the colon [12, 19].

Probiotics are defined as "live microorganisms that confer a health benefit on the host when they are administered in adequate concentration". Probiotics are mainly bacterial strains, mostly *Lactobacillus* or *Bifidobacterium*. Multiple studies in humans [20, 21] show the beneficial role of bacteria in the gastrointestinal tract. They were shown to be beneficial for inflammatory bowel disease; however, their use in pathologies such as cardiovascular diseases and CKD needs to be studied [22, 23]. Probiotics produce bacteriocins that inhibit the proliferation of pathogenic bacteria, increase the degradation of waste molecules, decrease the inflammatory response by blocking receptors, and participate the in immune response, thus reestablishing gut mucosa permeability [24].

Uremic toxins

Accumulation of toxic substances during CKD is common, and they are responsible for numerous symptoms and clinical complications during ESRD. Urea is the primary waste product in the kidney, and it is significantly increased in the

plasma of these patients. All waste molecules that derive from kidney failure are called UT, even if their metabolism or production did not depend on urea metabolism or their biosynthesis in the kidney. Approximately 90 different toxic substances have been described that result from reduced kidney functions or increased urea concentration in the gut epithelium. Various efforts focused on reducing their production or increasing their elimination from the human body; however, because most bind covalently to plasma proteins, this is a complicated task. Peritoneal dialysis or hemodialysis can only partially remove them [25].

High blood urea concentration in CKD increases gut permeability and leads to a toxic environment that induces the colonization of bacteria that express ureases and uricases to reduce urea concentration by conversion to ammonia; however, this ammonia increases the gut pH, facilitating the increase of pathogen bacteria originating dysbiosis, see Fig. 1. The main UT produced by intestinal microbiota are p-cresyl (PC), p-cresyl sulfate (PCS), p-cresyl-glucuronide (PCG), indoxyl sulfate (IS), indole-3-acetic acid (IAA), trimethylamine *N*-oxide (TMAO), and oxalic acid (OA) [26, 27].

p-Cresyl sulfate is produced by anaerobic bacteria in the gut, mainly by those bacteria that can degrade phenylalanine and tyrosine from the diet. Once PC is absorbed, it is conjugated with other substances in the liver, where a sulfate group is added; furthermore, PC suffers glucuronidation in the enterocyte given PCG. These products are usually eliminated in the urine through tubular secretion. Nevertheless, in CKD, these waste products accumulate in plasma increase the risk to development of cardiovascular and kidney diseases [8, 9, 28]. In a CKD rat model,

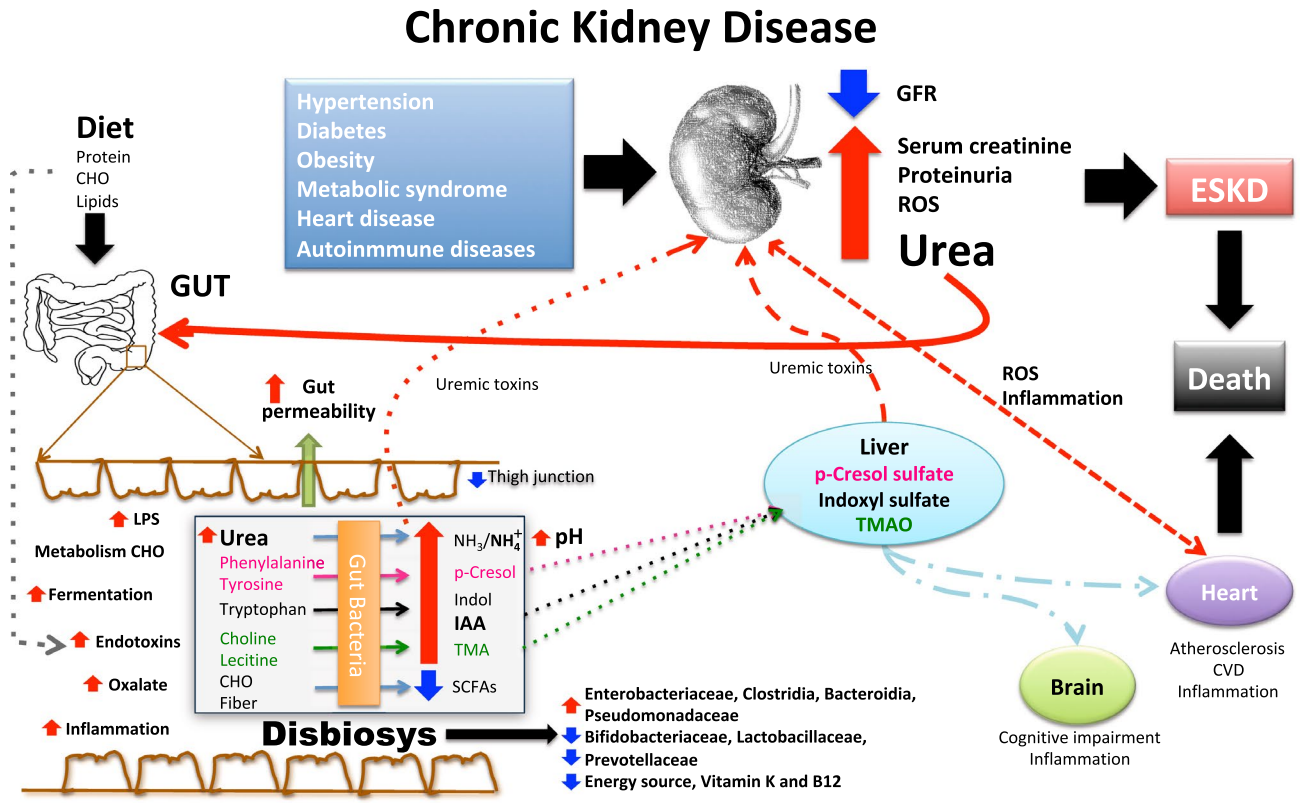

Fig. 1 Production of uremic toxins during chronic kidney disease. Loss of renal function increases the accumulation of waste molecules as creatinine, urea in the bloodstream; this effect induces the loss of urinary proteins and an increase in ROS generation. The high urea concentration induces changes in gut microbiota. Urea increases gut permeability by reduction tight junction proteins. The excessive amount of urea modifies the microbiota phyla, and increasing those bacteria than can metabolize urea. Metabolism of urea increases, and gut pH favoring enterocolitis. Diet as well as urea increase uremic toxin production, perpetuating organ damage and reducing SCFAs production that is the energy source, and they have been related to anti-inflammatory effects. The main uremic toxins or precursors, as PC, Idol, Indole acetic acid IAA, trimethylamine [36], PCS, IS, and TMAO, are produced by modified gut microbiota. UT are absorbed and transported to the liver, where they are distributed to other organs, including the kidney. Uremic toxins induce damage in endothelial cells, and they also induce brain inflammation; their presence in the hearth is involved with the development of atheroma as well as the oxidative stress, which leads to a pro-inflammatory and pro-fibrotic environment. The increase of uremic toxins induced both by diet transformation or by kidney dysfunction contributes to exacerbating the renal damage by activating a permanent state of inflammation, also increasing an oxidant millieu that leads the fibrosis in kidney and heat that culminate in ESRD or death

PCS increased the production of reactive oxygen species (ROS), activating nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and increasing the caspase 3 activity, which leads to an increased apoptosis ratio [29]. In vitro studies using HK2 cells found that PCS induces senescence through a reduction in Klotho expression [30].

Indoxyl sulfate and IAA are small molecules produced by gut bacteria that express the tryptophanase enzyme, which is capable of metabolizing the tryptophan and transforming it into indole; indole can be metabolized in the gut into indole-3 acetic acid, and it is also transformed into indoxyl sulfate in the liver. IS and IAA are the primary targets of the aryl hydrocarbon receptor (AhR) activation can lead to activation of the inflammatory cascade activating the nuclear factor kappa-light-chain enhancer of activated B cells (NFkB), increasing interleukin adhesion molecule expression. In the gut, IS increases permeability by the reduction of tight junction components such as occludin and claudin-1. It is also involved in free radical production; recently, the increase of IS or IAA was shown to be involved with atherogenic disease development and to increase the risk of developing cardiovascular disease [8, 9, 28, 31–33]. In the hearts of CKD patients, the uptake of IS is also mediated by organic anion transporter (OAT) isoforms 1 and 3, increasing the ROS production and reducing the NADPH activity. The elevation in ROS leads to the activation of mitogen-activated protein kinases (MAPK) p38 and p42/p44, which induces a release of pro-inflammatory and pro-fibrotic cytokines such as transforming growth factor beta (TGF-β) and alpha-smooth muscle actin (α -sma), leading to fibrotic events [34, 35], see Fig. 1.

TMAO can be ingested in the daily diet, but it can also be synthesized from choline, phosphatidyl-choline, L-carnitine, and lecithin metabolism by gut microbiota. The first stage is producing trimethylamine [36] in the gut. Then, TMA is absorbed and oxidized in the liver by flavin monooxygenase enzyme, producing TMAO. High levels of TMAO are involved in cardiovascular damage, inducing atherogenic syndrome, which increases the risk of cardiovascular disease and death in ESRD patients [37–40]

OA: it is an end product of catabolism of amino acids and ascorbic acid mainly produced by the liver; however, it can be obtained in the diet [41]. In CKD patients was observed a significant increase in plasma OA concentrations similar to serum creatinine, it was described that OA increases due to high uremia and it could be stored in several tissues such as kidney, heart, muscle, and others. The increase of OA gut excretion has been related to oxalate deposition in the kidney leading inflammation and fibrosis and progressive renal failure; in addition, the high OA concentration has been associated with atherosclerosis, cardiovascular diseases, joint injury, and kidney stone formation [42–45].

CKD and microbiota

A decrease in GFR increases the production and accumulation of many toxic substances. Vanholder R. et al. [46] reported the production of at least 90 different toxic molecules in peritoneal dialysis liquid of patients with CKD in comparison with healthy subjects; some of the most abundant waste products were PCS, IS, free fraction of IAA, homocysteine, uric acid, and hippuric acid, many of them have low molecular weight and a great percentage of them are protein bound, their concentrations are widely variable, and however, their toxic effects are not described yet [46].

To understand how uremia changes the gut microbioma, Vaziri et al. [47] showed that patients with ESRD from different etiologies had changes in 190 bacterial operational taxonomic units (OTUs) compared with control subjects; the main changes occurred in the Pseudomonadaceae family. They observed augmented *Actinobacteria*, *Proteobacteria,* and *Firmicutes* (mainly *Clostridia*). Further analysis showed that CKD patients had an increase in pathogenic gut bacteria colonization; these new florae express ureases, tryptophanase, and enzymes that convert aromatic amino acids and produce PC or IS. These molecules worsen the status of CKD patients, and this phenomenon was confirmed in a CKD rat model. CKD was induced by 5/6 nephrectomy surgery; after 8 weeks of tracing, they observed changes in 175 OTUs, confirming that at least 81 had a twofold change with respect to healthy rats. The concluding remarks were that ESRD induce crucial changes in the urea concentration in the gut and those changes are responsible for the following: (1) growth of bacteria capable of using urea as an energy source; (2) hydrolysis of the urea, increasing ammonia production; (3) increasing the gut pH, causing lumen enterocolitis and gut permeability; and (4) increasing UT absorption. In consequence, all worsened renal function [47].

Another study was performed in CKD patients with to know whether the increase of urea during ESRD modifies or increases the population of gut bacteria capable of expressing uricases and ureases and whether their expression caused even more damage in the kidney. This study included 24 stable patients with ESRD from different etiologies. The gene analysis of microbiota showed that ESRD patients had 12 of 19 bacteria families with urease activity (*Alteromonadaceae, Cellulomonadaceae*, *Clostridiaceae*, *Dermabacteraceae*, *Enterobacteriaceae*, *Halomonadaceae*, *Methylococcaceae*, *Micrococcaceae*, *Moraxellaceae*, *Polyangiaceae*, *Pseudomonadaceae*, and *Xanthomonadaceae*), at least five families with uricase activity (*Cellulomonadaceae*, *Dermabacteraceae*, *Micrococcaceae*, *Polyangiaceae*, and *Xanthomonadaceae*), and

three families with tryptophanase activity (*Clostridiaceae*, *Enterobacteriaceae*, and *Verrucomicrobiaceae*); interestingly, they observed a reduction in the *Lactobacillaceae* and *Prevotellaceae* families. Those families express the butyrate kinase gene involved in protective processes [48].

Yacoub et al. [49] demonstrated that gut bacteria have a central role in IS production; they performed a study in which they colonized germ-free mice with mutant bacteria (Bacteriodetes theta Bt Δ1492). These bacteria have deleted the tryptophanase enzyme gene that regulates tryptophan (BT1492) conversion to indole. Germ-free animals were not able to produce IS after 28 days of inoculation in comparison with wild-type animals. In addition, they observed in specific germ-free animals that changes in diet can induce the growth of specific bacteria, mainly suppressing the growth of one kind of bacteria that express the tryptophanase gene; in consequence, significant reduction of IS production was seen, and all these results confirmed that the presence of the microbiota has an essential role in the production of UT [49].

Recently, Yeh et al. [50] 2016 reported that in 232 stage III–V CKD patients of approximately 50 years of age, the increase of the UT as PC and IS was positively correlated with the increase in cardiovascular risk, augmentation of vascular brain incidents, and increase in ROS production, possibly due to endothelial injury [50, 51]. There is further evidence that an elevation in PC concentration is directly related to the development of hypertension [52].

In a study by Jiang et al. [53], 52 CKD patients and 60 healthy subjects were included to understand changes in the gut microbiome. The authors showed that CKD increases the proliferation of bacteria which produce PC and express ureases. They observed the reduction of other fecal bacteria populations with respect to healthy subjects. It was observed that bacteria that produce butyrate diminished significantly, and this phenomenon was associated with a pro-inflammatory environment. All findings suggest that CKD status may influence the microbiome in two ways: increasing accumulation of UT and inflammation and promoting a reduction of renoprotective molecules [53].

Trimethylamine *N*-oxide was recently described as a risk factor in cardiovascular diseases; as a common cause of the development of intestinal inflammation, atherosclerosis, and renal fibrosis, it also increases the risk of death during chronic renal disease. To understand TMAO levels during CKD, Xu et al. [54] analyzed 32 ESRD patients divided into two groups. The first group had higher GFR (7 ml/min/1.73 m^2) and the second had lower GFR (< 7 ml/min/1.73 m^2); a third group contained 32 healthy subjects. They found that both CKD groups had elevated classical injury markers blood urea nitrogen (BUN) and creatinine with respect to the control group, but no differences were observed between high or lower GFR groups. In addition, they found an increase in TMAO, L-carnitine and Cystatin C levels with respect to the control group; these results suggested that TMAO metabolism was activated. The stool analysis confirmed an increase in *Enterobacteriaceae* and a reduction in *Lactobacillus* phyla in this population, as previously shown [47]. The genetic analysis showed changes in at least 30 genes related to choline, betaine, and L-carnitine metabolism, and only eight genes had a significant difference compared with healthy subjects. These genes were involved in TMAO biosynthesis; some of them downregulated, such as phosphatidyl-choline acyltransferase, phosphatidyl-choline synthase, and choline monooxygenase, and others, were upregulated, including cytochromes 1 and 2. Those results suggest that CKD patients had altered gut microbiota, resulting in the overproduction of TMAO in the intestinal tract and leading to several complications in CKD patients [54].

The importance of microbiota was probed in an animal model of CKD. Mishima et al. [11] performed a study using germ-free (GF) animals; they induced CKD by adenine administration for 5 weeks. After this period, animals that had renal failure (GF-RF) presented lower kidney weight compared with GF animals, as well as an increase in fibrosis area, BUN, and serum creatinine, indicating that the CKD model was working. They also included a specific pathogen-free animal with CKD (SPF-RF), and this group had lower BUN levels than the GF-RF group. The authors quantified 180 UT in plasma, urine, and stool; they observed that GF-RF animals had fewer UT compared with the SPF-RF animals, and they were able to identify 11 toxins present in both GF-RF and SPF-RF animals, demonstrating that these toxins are produced even when gut bacteria are missing. These UT were classified into three groups: the toxins produced by gut microbiota, toxins that were the product of kidney disease by the metabolism of the host and gut bacteria, and toxins produced by microflora or diet consumption. These results revealed that the microbiome has an important role in CKD progression; when it is absent, there is a reduction of urea and amino acid utilization and SCFAs production in the gut is reduced. Reduction in consumption of these molecules promotes the toxic uremic environment due to the reduction in SCFAs production related to the anti-inflammatory and antifibrotic effects [11].

An observational study used HEMO (hemodialysis study) and CHOICE (Choices for Healthy Outcomes In Caring for ESRD) cohorts with the goal of understanding free PCS concentrations and their association with infections and sepsis in patients with ESRD. All patients were in dialysis treatment for at least 3–4.5 years. A total of 393 patients from CHOICE and 347 patients from HEMO studies were included, and they were stratified in tertiles according to the presence and degree of gastrointestinal disease (GI). The multivariate analysis from the CHOICE cohort revealed that high IS and PCS plasma concentrations from patients in the third tertile with GI led to

50% of the risk of developing infections and sepsis compared with the lower tertile of patients without GI. In addition, a positive trend between sepsis development and high levels of PCS in patients without GI was observed in both cohorts. These results suggest a strong association between higher concentrations of free PCS and infection-related or sepsis-related hospitalization in HD patients, showing the importance of microbiota in CKD [55].

A transverse study of 29 patients with stage III–V CKDin HD and 21 healthy subjects were performed. CKD patients were classified according to their stage of CKD or ESRD. All CKD patients underwent HD [56] for at least 10.2 years. As expected, HD patients had significantly increased serum creatinine (SCr) and urea compared with no dialysis subjects, and the UT were also higher than in control subjects. The inflammation markers interleukin 6 (IL-6) and monocyte chemoattractant protein-1 (MCP-1) were increased in HD subjects and had a direct correlation with IS plasma levels; these data suggest that elevation in the concentrations of UT could promote kidney damage by activation of the inflammatory pathway, which could be related to the development of cardiovascular diseases [31].

In a cross-sectional study made in 50 patients in HD, was evaluated the concentration of plasma OA and the presence of fecal Oxalobacter formigenes, to explain the accumulation of OA in CKD and its possible association with endothelial dysfunction. The authors were able to isolate O formigenes just from two HD patients and they found a direct correlation of OA concentration and aortic stiffness. Result suggests that in CKD, OA degradation is reduced by decrease of O formigenes colonization, the causes could be the use of antibiotics, or by changes in gut pH; it was suggested that the treatment with yogurt or kefir could correct this anomaly due to some strains of lactobacillus and bifidobacterium are capable of metabolizing OA and reducing their plasma concentrations [43, 44, 57].

Thus far, various experimental and clinical trials showed the importance of gut microbiota, and some studies probed the critical role of the gut in the production of UT, see Tables 2 and 3. Other authors consider that the lack of gut microbiota can worsen the CKD prognosis; certainly, dysbiosis has an essential role in many diseases, particularity in ESRD, in which the overproduction of urea promotes disequilibrium in normal flora that increases pathogenic bacterial and reduces protective bacterial proliferation, also increase the oxidative environment and potentiate the inflammatory environment.

Prebiotics and probiotics during CKD

Several efforts have been made to improve the quality of life of CKD and ESRD patients to prevent more comorbidities and increase lifespan. One of these efforts introduced the use of prebiotics and probiotics to increase the urea metabolism and reduce the production of UT. Tables 4 and 5 show some of the microbiota intervention studies performed in the CKD population as well as in experimental models.

One of the first efforts to introduce the concept of probiotics and its benefits to the regular diet in healthy and CKD individuals was the introduction of yogurt and fermented milk and kefir. All of them have been considered as functional foods, because they contain several strains of bacteria, yeast, or even fungi that improve the health status [58]. For example, in the diabetic or obese population, adding yogurt in their daily diet improves the fasting glucose levels and oxidative environment [59]. In a recent study made from the NHANES (1994–2014) results, the metabolic indexes and obesity with respect to probiotics exposition were evaluated. The authors found that those people who were exposed to probiotics including yogurt had less prevalence of comorbidities as hypertension, obesity, and diabetes; these results indicating that yogurt-probiotics have beneficial effects when they are included in daily diet [60]. Although the diabetic population is not the interest of this review, it is well known that higher percentage of them will develop CKD. However, the use of prebiotics and its role in this population is controversial, because in a meta-analysis performed by Barengolts et al. [61], where the effect of probiotics over glycemia and insulin resistance was analyzed the author, concluded that yogurt or kefir does not have any effect of reducing the fasting blood glucose, insulin resistance, or renal inflammation contrary, as it was reported in rat models [62–64].

To determine whether the reduction in uremic molecules has a beneficial effect, Sirich et al. [65] studied the diet supplementation of resistant starch (high amylose corn starch containing 40% digestible starch and 60% starch that is resistant to digestion) in a fiber form, which was administered to CKD patients included in HD therapy. After 6 weeks of starch supplementation, the authors saw a reduction in levels of urea waste products such as IS and PC; these results showed that fiber addition in CKD patients improves renal function by the reduction of UT in the gut, and this could be a beneficial supplement to treatment in these patients [65]. In addition, Vaziri et al. [66] demonstrated that 5/6 nephrectomized rats fed a high amylose resistant starch diet (HAM-RS2) for 6 weeks exhibited significantly reduced SCr and BUN. Furthermore, they observed that HAM-RS2 reduced the tubular injury in CKD animals compared with control animals. This phenomenon reduces colon permeability and reabsorption of UT in the gut, and this could also be mediated by microbiota due to changes in microbiota composition.

In another model of CKD induced by adenine administration, Kieffer et al. [67] observed that rats fed with HAM-RS2 for 3 weeks displayed reduced the production

Table 3 Identification of uremic toxins in experimental models during CKD

Study and stage CKD	Kidney markers	Uremic toxins	Main remarks
Mice 5/6 nephrectomy of APOE$^{-/-}$ with PCS administration. Atherosclerosis model [93]	**SCr**	**PCS** **Atheroma index in aorta** **α-sma** **Fibrosis**	The increment of PCS increases atheroma development and the apoptosis index in vascular smooth muscle cells. The connection between CKD and development of CVD
Mice 5/6 nephrectomy + PCS Relation of CKD with CVD development [29]		**PCS** **Apoptosis** **Fibrosis** **ROS**	Increase of PCS induces oxidative balance and contributes to the detriment of heart function in a CKD model
Rat renal tubular epithelial cells (NRK-52E cells) incubated in the presence of IS [94]	**LDH**	**Proliferation** **Migration** **α-sma** Cadherin **Apoptosis**	IS induced kidney damage by inducing changes in epithelial cell phenotype, increases in apoptosis and activation of MAPK and reduction of adherent proteins
Rats with nephrectomy 5/6 Administration with indoleacetic acid (IAA) or hippuric acid (HA) [95]	**MAP** **SCr (HA)** GFR **NAG** **Fibrosis**	**Tryptophan (IAA)** **IS (IAA)**	Overload of uremic toxins increase kidney damage, accelerating structural damage, fibrosis and sclerosis index
Human proximal tubular HK-2 cells Incubated with IS and IAA [92]		**ROS** **PAI-1**	IS and IAA induce ROS production and expression of PAI-1, activating NFkB Leading to a pro-inflammatory state that could contribute to kidney damage
Mice 5/6 nephrectomy [96]	**SCr** **Urea**	**IL-6** Intestinal motility **iNOS**	Spermine reduces intestinal motility and increases constipation. Antibiotics restores gut contraction without improvement in kidney failure

Bold indicates a significant increase of these parameters. Underlined characters indicate a significant decrease of these parameters

Table 4 Main changes after prebiotic and probiotic intervention clinical trials in patients with CKD

Model	Treatment	Uremic toxins	Kidney	Gut
Uremic non dialysis patients with GFR <30 ml/min [77]	Adsorbent AST-120 + low protein diet 48 h	IS PCS	IS PCS	
HD patients [65]	Prebiotic. 15 g high amylose corn starch (Hi-maize-260). 6 weeks	IS (free) 30%, IS (total) 17% PCS (free) 14% Albumin 9%		
CKD patients stage (IV–V) [82]	Prebiotic. High molecular weight inulin, fructooligosaccharides Probiotic: *Lactobacillus, Bifidobacterium and Streptococcus*. 4.5×10^9 CFU. 6 weeks	PCS 22% IS 28%	GFR = Inflammation=	***Bifidobacterium*** ***Lactobacillus*** ***Lachnospiraceae*** ***Faecalibacterium*** *Ruminococcaceae* *Clostridium*
CKD patients stage III–IV. Non-dialysis [97]	Probiotics. Fermented dairy drink. *L. casei*, 8×10^9 CFU. 2 months		Urea GFR =	
CKD stage III–V patients non-dialysis [81]	Low protein diet + prebiotic + probiotic. *S. thermophilus, L. acidophilus* and *B. longum*, 4.5×10^9 CFU each 6 months		Delayed GFR fall	
CKD patients on HD [98]	Probiotics. *L. acidophilus, L. casei, B. bifidum.* 2×10^9 CFU. 12 weeks	Glucose Insulin Oxidative stress	No renal changes	**Nutrition status**
CKD patients stage III–IV. HD [24]	Probiotics. 3 months 3 capsules/day 9×10^{13} CFU. *S. thermophilus* (KB19), *L. acidophilus* (KB27), and *B. longum* (KB31)	TMAO =	GFR = **Betaine**	
CKD stage IIIa patients [83]	Low protein diet + probiotics 2 weeks colonization and 3 months of maintenance. Bifiselle® Bromatech (Enterelle® Bromatech) 2 capsules/day	Indican CRP Cholesterol	GFR =	***Lactobacillus*** ***Bifidobacterium***
CKD patients stage III–V non-dialysis [99]	Prebiotic. 12 g NutraFlora^R P-95 + low protein diet. 3 months	PCS 14% HDL-C	GFR = Proteinuria =	
CKD patients at least 3 months in HD [100]	Symbiotic: Probiotic® Bisflora 2×10^7 CFU each and prebiotics. Fructooligosaccharides inulin and, galactooligosaccharides 5 g each 3 months	ICAM VCAM	No renal changes	
ESRD patients on HD [101]	Symbiotic: Probiotic. *L. acidophilus and B. Bifidus,* 2×10^{12} CFU Prebiotics. Inulin, Omega 3- fatty acid and vitamins (B complex, C, E and folic acid) 2 months			*C. leptum* Lactobacillus **Bifidobacterium**
ESRD patients on HD [102]	Prebiotic. Fermentable soluble fiber supplementation. 10–20 g day. 6 weeks		IL-6 TNF-α CPR Cholesterol Oxidative stress	
CKD patients stage III–V Non-dialysis [103]	Probiotic. *S. thermophilus* (KB19), *L. acidophilus* (KB27), and *B. longum* (KB31) 9×10^{10} CFU 2 capsules each meal. 3 months, crossover 3 more months		BUN	Cecal pH
CKD patients on HD [104]	Probiotic. *Lactobacillus rhamnosus.* 1.6×10^7 CFU. 28 days	PC Phenol	No renal changes reported	
ESRD patients on HD [68]	Prebiotic. HAM-RS2. 20 g 1 month and 25 g second month	–	BUN IL-6 TNF-α	**Faecalibacterium**

Table 4 (continued)

Model	Treatment	Uremic toxins	Kidney	Gut
ESRD patients on dialysis [105]	Probiotics. Renadyl® 2 capsules/day 30×10^{12} CFU *S. thermophilus* (KB19), *L. acidophilus* (KB27), and *B. longum* (KB31) 2 months	UT=	CPR= TIG=	
CKD patients on HD [106]	Symbiotic. Probiotic daily milk drink *B longum* 7.4×10^8 CFU/100 ml Prebiotic 40 g of sorghum flakes. 7 weeks	IS IAA= PCS	Urea	**Acetic acid** **Butyric acid** **Propionic acid** **Fecal pH**
CKD patients on HD [107]	Probiotic. Capsules 500 mg containing *L. acidophilus, B. longum* and *S. thermophilus* 3×10^8–3×10^{10} CFU 12 weeks		CPR= Hemoglobin=	
ESRD patients on HD [108]	Prebiotic. HAM-RS2 25 g. 8 weeks	PC IS=	SCr Uric acid Urea=	

Bold characters indicate a significant increase of these parameters. Underlined characters indicate a significant decrease in these parameters

Table 5 Main changes after prebiotic and probiotic intervention experimental models ok CKD

Model	Treatment	Uremic toxins	Kidney	Gut
Rats Adenine CKD [66]	Prebiotic. High amylose maize (Hi-Maize 260) starch. 3 weeks		SCr, urea Proteinuria TIF Inflammation ROS, CCr	**Occludin** **Claudin 1**
Rats 5/6 nephrectomy [69]	Adsorbent activated charcoal AST-120, AST-120 + *L. acidophilus* 1×10^{10} CFU. 12 weeks	IS PCS IAA IL-6	BUN Proteinuria Sclerosis FTI	Occludin Claudin 1 TLR4 ***Lactobacillus***
Mice 5/6 nephrectomy ApoE$^{-/-}$ mouse [70]	Adsorbent activated charcoal AST-120, 18 weeks	IS Triglycerides Cholesterol	Ccr	
Mice Adenine CKD [71]	Adsorbent activated charcoal AST-120 8 g 4 weeks	IS PCS	IS PCS Inflammation GFR =	PCS
Mice 5/6 nephrectomy [109]	Probiotics. *L. rhamnosus and L. acidophilus*, 1×10^{11} CFU. 8 weeks	TNF-α IL-6 IL-10	MCP-1 SCr Proteinuria	*Clostridium* ***Lactobacillus*** **Claudin 1** Apoptosis Gut permeability
Rats 5/6 nephrectomy [110]	Prebiotic. Oligosaccharides Probiotic. 1% *B. longum* 8 weeks	IS= Pi iPTH	SCr BUN	***Bifidobacteria*** *Ruminococcus* *Clostridium* *Turicibacteria*
Mice Adenine CKD [111]	Prebiotic: laxative linaclotide 10–100 mg/kg 2 weeks	TMAO IS Hippurate	SCr BUN Uric acid Fibrosis Inflammation	***Clostridiales*** ***Dehalobacterium***

Bold characters indicate a significant increase in these parameters. Underlined characters indicate a significant decrease in these parameters

of UT in comparison with CKD animals. HAM-RS2 improved the hydration status of all animals; the cecal content showed that HAM-RS2 modified 44% of the bacteria composition with respect to CKD animals. The authors found that relative abundance of *Actinobacteria* and *Proteobacteria* was increased, whereas Firmicutes abundance

was significantly reduced in HAM-RS2-treated animals vs. CKD rats. Remarkably, the *Bacteriodetes*/*Firmicutes* ratio was increased; in other words, HAM-RS2 preserves the beneficial bacteria that promote UT molecule utilization to reduce circulating urea, leading to lower loads in the kidney for reducing inflammation and oxidative stress.

Interestingly, HAM-RS2 was able to reduce the production of the toxic metabolites serum creatinine, hippuric acid, urea, uric acid, putrescine, myoinositol, and phenol. The mechanism proposed was that HAM-RS2 could increase urea transporter expression and amino acid utilization. Another explanation is the increase in the concentration of SCFAs such as butyrate that is known to have renoprotective effects; an alternative mechanism could be that the maintenance of intracellular gut pH could reduce gut fermentation. Finally, the authors suggest that this fiber can be added to yogurt or juice for introduction into the regular diet of CKD patients and delay the progression of CKD [47, 66, 67]. Recently, HAM-RS2 was probed in an RCT, where 20 HD patients were included; after 2 months of treatment, it was observed that HAM-RS2 was able to reduce BUN, IL-6, and TNF-α levels in HD patients, and fecal analysis shown that Faecalibacterium genus was increased in this group, suggesting that resistant starch increases the SCFAs' production [68].

The use of chemical adsorbents has also been tested. Yoshifuji et al. [69] used the activated charcoal pellets AST-120 to reduce UT in rats with CKD. Rats with 5/6 nephrectomies were treated with AST-120 for 12 weeks. The treated animals had a significant reduction in proteinuria and BUN without changes in serum creatinine. In addition, the authors observed a slight reduction in renal fibrosis area, which was followed by a reduction in the plasma UT, IS, and PC. In the renal structure, the authors observed that AST-120 restores the adherent tight junction proteins claudin-1 and occludin in the gut; this effect was significantly associated with the reduction of urea reabsorption and also re-established part of the microbiota family *Lactobacillus*, suggesting that gut urea absorption has an essential role in the development of the renal disease. Likewise, Suguru et al. [70] reported that AST-120 in CKD Apolipoprotein E deficient mice reduced the urinary IS levels and the risk of developing atheroma or cardiovascular disease; they observed that this compound significantly reduced the inflammation cascade TNF-α, interleukin 1β (IL-1β), and MCP-1 [70].

Another study by Sato et al. [71] evaluated AST-120 in mice with CKD induced by adenine administration and reported reduced levels of IS and PCS in plasma, kidney, spleen, muscle, and testis compared with wild-type mice. The authors showed that AST-120 did not modify creatinine or BUN. The concluding remarks were that UT accumulates in different organs, and AST-120 administration diminished them and reduced multiorgan failure in CKD patients [71].

An experimental study performed in rats with CKD induced by adenine diet, and the authors show that the administration of Acacia gum (AG) as prebiotic reduces the kidney injury. AG has a high content of soluble fiber, and it is rich in polysaccharides, which has been used with success in CKD rat models. AG was able to reduce BUN and serum creatinine as well as inflammatory and oxidative markers; in addition, it was observed a significant reduction in plasma IS levels [72–74]. Further studies performed in diabetic rats with or without CKD were shown that acacia gum administration reduced the BUN, serum creatinine, NGAL, and cystatin C, in addition, the IS levels were reduced in both diabetic and CKD rats, and similarity AG was able to reduce inflammation markers as TNF-α, IL-1β, and the fibrosis levels. The protective effects could be mediated by the activation of anti-inflammatory and antioxidant pathways, and it also was described that AG could have prebiotic action by the interference in indole production or by their later absorption in the gut [75].

To determinate the mechanism by which dysbiosis contributes to CKD progression, in 5/6, nephrectomy rat model was demonstrated that CKD induces the presence of 291 metabolites in serum, and their levels were correlated with changes in fatty acid metabolism, amino acid metabolism, polyamine, and purine metabolism, and most of them were associated with gut metabolism. These observations were associated with changes in different microbial genera determinated by 16S rRNA gene sequencing of fecal samples. The proteomic analysis showed that dysbiosis induced changes in polyamines and glycine metabolism and was directly correlated with the increase in SCr and systolic blood pressure worsening kidney health; the intervention with poricoric acid (PA) isolated from Poria *cocos* (fungal mushroom), as prebiotic during 12 weeks was able to reduce the kidney damage. Prebiotic treatment improved glycine and polyamine metabolism and also improved renal function reduced SBP, fibrosis score, inflammation, and oxidative stress due to the reduction of polyamines as hippuric acid, spermine, spermidine, acrolein, and putrescine among others [76].

Niwa et al. [77] studied the effect of reducing uremic toxic molecules by a reduction in protein consumption and supplementation with prebiotics. They identified that probiotics reduced the concentration of PC to the same extent as the low protein diet. However, the low protein diet increased the malnutrition status, which could increase the death risk in these patients [78].

Using Arabic gum as prebiotic was determinate in an open-label randomized trial, where 36 patients in stages 3–5 of CKD were included. The treatment consists of oral administration of 10, 20, or 40 g of soluble Arabic gum daily along 4 weeks. The conclusion was that Arabic gum reduces the pro-inflammatory environment in these patients

without modifying renal function [79]. Applying resistant starch (Hi-Maize) as prebiotic was proved in a randomized pilot controlled trial, where 43 HD patients were included. They received Hi-Maize® 260, Ingredion, USA, or placebo for 4 weeks. Renal parameters did not change in both groups; however, the fiber intake increases 85% in the Hi-Maize group. The supplementation with resistant starch reduced the T-BARS, IL-6 levels in the CKD group significantly. This phenomenon was observed with IS without changes in PCS levels, and although the protective mechanism is unknown, the author suggests that could be mediated by changes in microbiota, probably due to starch will promote the Lactobacterium and Bifidobacterium colonization or inducing SCFAs' production [80].

Recently, the introduction of probiotics has been used as an alternative therapy in the CKD population. Pavan et al. [81] performed a study in patients with stage III–V CKD without replacement therapy. They included 24 CKD patients randomly divided into the following two groups: the first group received a low protein diet (0.6 g/kg/day) plus prebiotics (Fructooligosaccharides, 100 mg) plus probiotics [*S. Thermophilus*, *L. acidophilus,* and *B. longum*, 4.5×10^9 colony forming units (CFUs) each] in 3 pills/24 h, and the second group only received a low protein diet. All subjects were monitored for 6 months. The results did not show changes in any biochemical parameter that reflects an improvement in CKD; however, the authors observed that the decline in GFR progression was lower in the low protein + pre/probiotic group vs. the low protein group. They concluded that maintaining the microbiota could be a therapeutic option in this population [81].

Other of the first trials was the SYNERGY (Synbiotics Easing Renal Failure by Improving Gut Microbiology) study, a double-blind, placebo-controlled crossover trial that included 37 stage IV CKD patients. All patients were advised to eat a low protein diet for 2 weeks and then were randomized in two groups: the first group received placebo, and the second group was supplemented with 15 mg/day prebiotic and 4.5×10^9 CFUs from 9 different strains, mainly *Lactobacillus* and *Bifidobacterium*, for 6 weeks, which was followed by 4 weeks of wash out and then 6 weeks with the opposite treatment. The main outcome in this trial was 22% to 28% reduction in PCS and IS in patients treated with symbiotics; the authors did not observe changes in GFR, kidney injury molecule (Kim-1) levels or changes in pro-inflammatory markers, but they observed a better nutritional status in this population, because serum albumin was higher and there were no changes in proteinuria, which suggested no CKD progression. In addition, fecal PCR showed that symbiotic treatment significantly increased the abundance of *Bifidobacterium* by 3.2%, which was a fivefold change vs. placebo group; the same effect was observed with *Lachnospiraceae*, which showed a 2.1% increase. A reduction of 4.3% in the *Clostridia* family was seen. This result indicates that the microbiota prevents the CKD progression, which could be due to probiotics modifying the gut bacteria and promoting the metabolism of UT [82].

Simeoni et al. [83] studied the impact of probiotics in stage III CKD patients who were over 18 years by administering 45–60 ml/min GFR and standardizing the protein consumption in these patients to 0.7–1 g/kg/day. Patients were randomly divided into two groups: the placebo group and the probiotic group. The probiotic group received the following three schemes of probiotic treatment for a duration of 3 months: they started supplementation with one capsule of probiotics every day for a week, followed by 2 weeks with six capsules daily at each meal (one of them was Bifiselle® Bromatech and the other Ramnoselle® Bromatech); the third stage of probiotic supplementation included two capsules of probiotics for 3 months. At the end of the experimental period, the authors observed increases in the CFU of *Lactobacillus* and *Bifidobacterium* in the probiotic group respecting to the basal period and concerning to the placebo group. They quantified the Indican levels (UT) and they observed a significant decrease of it in the probiotic-treated group; in addition, the probiotic supplementation reduced cholesterol and triglycerides in these patients, and these changes were associated with the reduction of fermentation and putrefaction. The authors concluded that probiotics restored the gut microbiota, improving urea utilization and reducing the kidney injury. In addition, they found that a reduction in indican levels was associated with a reduction of cardiovascular disease risk. Finally, they speculated that probiotic intervention in early stages of CKD would help to delay progression of CKD, and the use of this supplementation needs to be studied in patients with stage IV and V CKD [83].

Recently, Borges et al. [24] tested the effect of probiotic supplementation to reduce TMAO in HD patients. A total of 21 patients were included in two groups: 11 patients were supplemented with 9×10^{13} CFUs of *Strep. thermophilus*, *L. acidophilus,* and *B. longum* every 24 h for 3 months, and the remaining ten patients were administered placebo and followed for the same amount of time. All patients were classified as stages III–V of ESRD. The authors did not find any change in TMAO levels between groups; in addition, all kidney damage markers were identical in both groups. They observed a significant increase in betaine concentration; this molecule is involved in decreasing fat mass and reducing body weight in diabetic populations and could play a role in CKD. The authors consider that this study has several limitations, including the small sample size, the probiotics concentration, and the time of supplementation. It will be necessary to perform many more trials to know whether the microbiota has a protective role in HD patients with CKD [24].

A recent meta-analysis performed by Thongprayoon et al. [84] in five randomized controlled trials, where CKD patients were studied. The outcome was to found an improvement in renal function as well as UT reduction. Probiotics were prescribed for four until 6 months; the amounts of bacterial CFUs and strains were diverse, nevertheless; the most common bacteria were Lactobacillus and Bifidobacterium. There were no differences in GFR, serum creatinine or BUN basal, and post probiotic treatment, but they observe a significant reduction in PC, demonstrating that probiotics could have a beneficial role in CKD. In a further meta-analysis, the authors try to assess the role of microbiota improvement over the UT, inflammation pathway or in the gastrointestinal tract symptoms (GYS) in ESRD patients, the authors finally include 7 clinical trials that meet all inclusion criteria, 178 ESRD in dialysis were studied, all of them received probiotics and some prebiotics, the treatment period was variable from 2 weeks until 6 months, again, the probiotics more used were Bifidobacterium and Lactobacillus. At the end of the analysis, the authors were capable of showing that probiotics reduced significantly the CRP level postprobiotic treatment. In addition, they observed a reduction in UT, and they find that probiotic supplementation improves all the GYS. They may not observe kidney function improvement, though the reduction of uremic and inflammation combined with GYS to recovery improves the general quality of life [85]. Another meta-analysis including eight controlled clinical trials with 230 patients under dialysis, where the primary outcome was to find out if probiotic supplementation improves renal function and anemia or reduces uremia and inflammation. The results showed that probiotic supplementation did not reduce SCr, BUN, Hb, or IL-6, but the addition of probiotics was able to reduce PCS levels in CKD, which is related to reduce uremia toxic effects and prevent cardiovascular events in this population [86]. In a recent meta-analysis realized in ten RCTs, Sibei Tao et al. found that probiotics did not have a beneficial effect on dialysis patients. Nevertheless, their results showed that BUN levels were reduced by probiotic administration in non-dialysis CKD patients concluding the necessity of a well-designed study to evaluate probiotics effectiveness in the CKD population at least in early stages [87].

In a very recent double-blinded study performed in 46 HD patients, a probiotic scheme was directed. Half patients received placebo and the other half probiotic (9×10^{12} CFU) in tree capsules every 24 h along 3 months (Prebiotics were *Streptococcus thermophilus*, *Lactobacillus acidophilus*, and *Bifidobacteria longum.* The adherence to the protocol was 82%; however, no changes in plasma markers were observed; on the other hand, the fecal pH in the probiotic group was reduced. The authors suggest that probiotics administration is a big issue that needs to be clarified, so that it could be used as treatment in HD patients due to IS increase in the probiotics group. They and other researchers observed this result and they suggested that this phenomenon could be originated by bacterial gut overproduction in the gut, leading an increase of gut permeability of IS and NH_3^+ to the bloodstream generating a toxic environment that could increase urea through urea cycle in the liver and increasing circulate uremic toxins. The difference between experimental and clinical probiotic studies could be the environment factors mediated by food intake and polypharmacy that accompanies CKD patients as well as the size of the study [88].

Similar effects observed de Faria Barros. et al. [89] in a double-blind, randomized placebo-controlled trial, with 30 non-dialysis CKD patients, after 30 days of probiotic, they did not observe any change in renal function or uremic status, they observed an increase in IL-6 circulating levels, concluding that probiotics do not have any helpful effect in CKD patients, and however, the main limitation of this study was the sample size [89].

Conclusions

CKD is a multifactorial disease associated with several other comorbidities that complicate its treatment. The alternative is the use of adjuvants therapies to avoid loss of kidney function.

The microbiota has been described as a significant contributor to the health status, because it helps by digestion absorption process to increase energy sources and for providing minerals, proteins, and some cofactors to the host. Dysbiosis increases the production of UT in CKD. The primary mechanism is that kidney dysfunction increases the urea concentration, leading to changes in gut flora. These changes favor some strains that can metabolize urea and its derivatives, increasing uremic molecule production and deteriorating kidney function. Uremia increases gut permeability, and this phenomenon could contribute to multiorgan failure. Probiotics mainly *Lactobacillus* and *Bifidobacteria* and prebiotics have been employed to change the gut metabolism in CKD, see Fig. 2. However, the results are still unclear, as many studies showed that probiotics reduced UT concentrations, the IS and PCS levels without changes in BUN, and serum creatinine; others report poorly support in the use of probiotics and show that they did not modify any kidney injury markers, although the supplementation prevented ESRD progression, improving glucose levels, and maintains hemoglobin and diminish inflammation environment contributed to a better quality of life in this population. It will be necessary to the study of the use of pre and probiotics in a larger sample size, and it will be crucial to identify the useful bacteria strains, as well as the dose and time of treatment, to affirm that they could be considered a beneficial complement to the treatment of CKD.

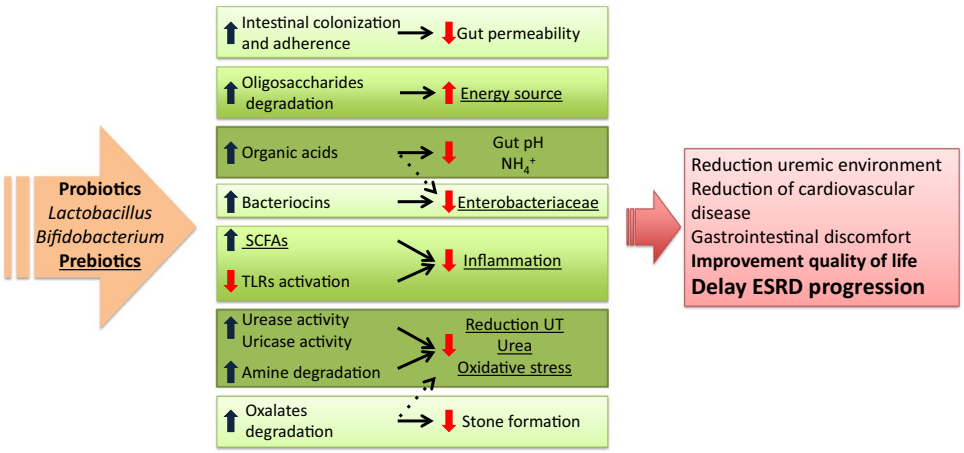

Fig. 2 Principal gut and metabolic effects induced by probiotic and prebiotics supplementation in the CKD population. Underlining indicates the effects described by prebiotic supplementation

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Compliance ethical standards

Conflict of interest The authors declare that there are no conflicts of interest.

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