nefrología
Revista de la Sociedad Española de Nefrología
www.revistanefrologia.com

Review

Gut microbiota in chronic kidney disease☆

Secundino Cigarran Guldris[a,*], *Emilio González Parra*[b], *Aleix Cases Amenós*[c]

[a] *Sección de Nefrología, Hospital Da Costa, Burela, Lugo, Spain*
[b] *Servicio de Nefrología, Fundación Jiménez Díaz, Universidad Autónoma de Madrid, Madrid, Spain*
[c] *Servicio de Nefrología, Hospital Clinic, Universitat de Barcelona, Barcelona, Spain*

ARTICLE INFO

Article history:
Received 8 March 2016
Accepted 10 May 2016
Available online 23 February 2017

Keywords:
Chronic kidney disease
Gut microbiota
Dysbiosis
Uraemic toxins
Inflammation

ABSTRACT

The intestinal microflora maintains a symbiotic relationship with the host under normal conditions, but its imbalance has recently been associated with several diseases.

In chronic kidney disease (CKD), dysbiotic intestinal microflora has been reported with an increase in pathogenic flora compared to symbiotic flora. An enhanced permeability of the intestinal barrier, allowing the passage of endotoxins and other bacterial products to the blood, has also been shown in CKD. By fermenting undigested products that reach the colon, the intestinal microflora produce indoles, phenols and amines, among others, that are absorbed by the host, accumulate in CKD and have harmful effects on the body. These gut-derived uraemic toxins and the increased permeability of the intestinal barrier in CKD have been associated with increased inflammation and oxidative stress and have been involved in various CKD-related complications, including cardiovascular disease, anaemia, mineral metabolism disorders or the progression of CKD. The use of prebiotics, probiotics or synbiotics, among other approaches, could improve the dysbiosis and/or the increased permeability of the intestinal barrier in CKD.

This article describes the situation of the intestinal microflora in CKD, the alteration of the intestinal barrier and its clinical consequences, the harmful effects of intestinal flora-derived uraemic toxins, and possible therapeutic options to improve this dysbiosis and reduce CKD-related complications.

☆ Please cite this article as: Guldris SC, Parra EG, Amenós AC. Microbiota intestinal en la enfermedad renal crónica. Nefrología. 2017;37:9–19.

* *Corresponding author.*
E-mail address: secundino.cigarran.guldris@sergas.es (S.C. Guldris).

Microbiota intestinal en la enfermedad renal crónica

Palabras clave:
Enfermedad renal crónica
Microbiota intestinal
Disbiosis
Toxinas urémicas
Inflamación

RESUMEN

La microflora intestinal mantiene una relación simbiótica con el huésped en condiciones normales, sin embargo, su alteración se ha asociado recientemente con numerosas enfermedades.

En la enfermedad renal crónica (ERC) se ha descrito una disbiosis en la microflora intestinal con un aumento de la flora patógena sobre la simbionte. Además, la permeabilidad de la barrera intestinal está aumentada, lo que permite el paso de endotoxinas y otros productos bacterianos a la sangre. La microflora intestinal, mediante la fermentación de productos no digeridos que alcanzan el colon, produce indoles, fenoles, o aminas, entre otros, que son absorbidos por el huésped, se acumulan en la ERC y tienen efectos deletéreos sobre el organismo. Estas toxinas urémicas generadas en el intestino y el aumento de la permeabilidad de la barrera intestinal en la ERC se han asociado a un aumento de la inflamación y el estrés oxidativo, y están implicados en diversas complicaciones asociadas a la ERC, como la enfermedad cardiovascular, la anemia, las alteraciones del metabolismo mineral o la progresión de la ERC. El uso de prebióticos, probióticos o simbióticos, entre otras aproximaciones, podrían mejorar la disbiosis o el aumento de la permeabilidad de la barrera intestinal en la ERC.

En este artículo se revisan la situación de la microflora intestinal en la ERC, la alteración de la barrera intestinal y sus consecuencias clínicas, los efectos deletéreos de las toxinas urémicas derivadas de la microflora intestinal, así como las posibles opciones terapéuticas para mejorar esta disbiosis y reducir las complicaciones de la ERC.

What are the microbiota and the microbiome?

Since Hippocrates (400 BC) established that "death lies in the intestines", their influence on the health of human beings has been well known.

The germs that inhabit our body are called the microbiota, and their collective genomes, the microbiome. More than 100 trillion germs (10^{14}) cohabit with us throughout our lives, representing 10 times the number of cells that make up our body and constituting 1.5–2 kg of our weight.[1,2] The concentration of germs in the digestive tract gradually increases from the stomach to the colon, where they reach the highest concentration (up to 10^{11} microorganisms/g of faeces) and diversity. The gut microbiota plays an important role in metabolic, nutritional, physiological, and immunological processes, and constitutes a true ecosystem.[3] The human microbiome is our second genome, which has more than 3 million genes (100 times more genes than the human genome itself) and is the subject of research by the Human Microbiome Project Consortium.[4–6]

Originally, the gut microbiota is formed through the placenta, where low levels of non-pathogenic germs, especially the phyla firmicutes, bacteroidetes, and *Fusobacteria* are nested. In the first years of life, feeding, type of birth, hygiene, and use of antibiotics condition the formation of the intestinal microbiome.[7,8] Different species of germs colonise and are originated during various events (Table 1).

The gut microbiota is established in the first 2–3 years of life as a dynamic ecosystem, dominated by bifidobacteria; their composition increases in richness and diversity until reaching their maximum complexity in adulthood, when the dominant species are bacteroidetes, firmicutes and actinobacteria.[9–11]

Table 1 – Intestinal microflora in relation to perinatal events.[4,5]

Exposure	Intestinal flora
Vaginal canal	*Bifidobacterium*, bacteroids, *Lactobacillus*, prevotella, enterococci, streptococci, *Clostridiaeceae*
Post-caesarean delivery	*Staphylococcus*, *Corynebacterium Propionibacterium*. Lower amount of *Bifidobacterium* and bacteroides
Breast-feeding	*Bifidobacterium*, bacteroides, *Lactobacillus*, clostridia, actinobacteria and firmicutes
Artificial breastfeeding	Bacteroides, clostridia, *Enterobacteriaceae*

Bacterial communities that lie in the intestine are, therefore, a combination of different types and amounts of bacteria and 3 different groups of microbiota or enterotypes have been identified in humans.[12] The phylogenetic composition of intestinal microflora tends to be similar between individuals from the same region, from the same family and also with a similar diet which plays a significant role in their composition.[13,14]

Dietary habits affect the composition of the gut microbiota. Since the microbiota is in contact with a significant number of neural cells and immunological cells, it directs the maturation of the immune system in childhood and contributes to the maintenance of its homeostasis during life.[2] Complex polysaccharides, which are not digested by enzymes

in the small intestine, are metabolised by the colon microflora. These polysaccharides are degraded and fermented in the large intestine and converted into short chain fatty acids (SCFAs) and gases (CO_2 and H_2). A high intestinal content of fructose promotes the formation of butyrate which is produced by bacteria. Dietary supplementation with specific polysaccharides may promote the growth of "healthy" germs (*Bifidobacterium*, *Lactobacillus*), the production of SCFA and it may decrease intestinal pH that inhibits the growth of pathogenic bacteria.[15,16]

In the ageing process, progressive damage occurs to the morphology and function of the different systems and the microbiota becomes less diverse and more dynamic, characterised by the predominance of bacteroidetes over firmicutes, with an increase of *Protobacteria* spp. and a decrease of *Bifidobacterium*. This is evidenced by rRNA techniques and it has been analysed as part of the study ELDERMET.[17–19] Major changes in the microbiota are found in the colon of persons over 60 years of age. The significance of these changes is yet to be clarified.[20]

Faecal bacteria such as *Escherichia coli*, which divides every 20 min, are genetically prepared to be highly adaptative, and always survive even though their host ages. Without this plasticity, we probably would not have been able to cope with changes in lifestyle and dietary habits, as evidenced by the transition from the Palaeolithic to the dietary habits of Western societies.[21]

Functionally, the gut microbiota provides nutrients and energy to the body through fermentation of nondigestible foods in the large intestine. The most important fermentation products deriving from the fermentation are the SCFA, which serve as a source of energy to intestinal cells and bacteria, and contribute to energy expenditure, satiety, and glucose homeostasis.[22] Other relevant functions of the gut microbiota are the endogenous synthesis of certain vitamins and amino acids, the metabolism of bile acids, or the maintenance of the integrity of intestinal barriers, which protect the host from pathogenic germs.

Thus, the gut microbiota is involved in the maturation of the immune system in infancy and contributes to the maintenance of its homeostasis throughout life.[23]

Gut microbiota in chronic kidney disease

From the early stages of chronic kidney disease (CKD) there is a quantitative and qualitative alteration of intestinal microflora (dysbiosis); so the composition and metabolic activities of microflora are changed in CKD and this is a hot and innovative topic in nephrology literature. These alterations include changes in intestinal transit, decreased protein absorption, decrease in dietary fibre intake, treatment with oral iron and frequent use of antibiotics.

All of this contributes to systemic inflammation and the accumulation of uraemic toxins that are absorbed by intestine and eliminated by the kidney. Inflammation and uraemic toxins play a central role in the pathophysiology of atherosclerosis, as well as in other complications associated with CKD[24–27]; that will be reviewed below.

Table 2 – Gut microbiota changes in CKD.

Intestinal tract	Normal	CKD/ACKD
Stomach	*Lactobacillus* *Helicobacter*	No change
Duodenum	*Staphylococcus* *Streptococcus* *Lactococcus*	Increased
Jejunum	*Enterococcus* *Streptococcus* *Lactobacillus*	Increased
Ileum	*Enterobacteriaceae* *Bacteroides* *Clostridium* Bacterial fragments	Increased
Colon	Firmicutes *Bacteroides* Actinobacteria Proteus *Clostridium* *Lactobacilli* *Prevotellaceae* *Fusobacterium* TM7	Increased: Proteobacteria, Enterobacteria, *E. coli*, Acinetobacter, *Proteus* spp. Decreased: *Lactobacillus*, *Bifidobacterium* spp. Aerobic overgrowth of at least 100 times Increase of *Clostridium perfringens*

CKD, chronic kidney disease; ACKD, advanced chronic kidney disease.

Patients with CKD are polymedicated. Some drugs frequently prescribed to these patients may alter intestinal microflora, especially antibiotics,[28,29] but others may also slow intestinal transit, phosphorus binders, ion exchange resins,[30] or iron supplements that may have an effect on microflora but it is not well defined.[31,32]

Change in intestinal barriers in chronic kidney disease

Changes in intestinal barriers with an increased intestinal permeability is common in CKD (Table 2).

Increasing urea levels and expanding bacteria with urease causes an increase ammonium production in the intestinal lumen and induce changes in intestinal pH that produces an alteration of intestinal permeability by affecting the tight junctions of the enterocyte. Vaziri et al. have demonstrated a marked reduction of tight junction proteins, claudin-1, occludin, and ZO1, in the colonic mucosa in CKD; this is associated with an infiltration of mononuclear leukocytes in the lamina propria and a marked thickening of the colon wall.[33] There is histological evidence of chronic inflammation of the intestinal tract including oesophagitis, gastritis, etc.[33,34]

The presence of frequent oedema and hypervolaemia in CKD may aggravate intestinal barrier dysfunction in CKD patients on, haemodialysis, or peritoneal dialysis. In addition, excessive ultrafiltration and episodes of hypotension during haemodialysis may cause episodes of transient intestinal ischaemia which increases the permeability of the intestinal barrier facilitating the passage of endotoxins.[33]

In renal transplant patients, the investigation of the gut microbiota is in its infancy. It is known that inflammatory processes, such as graft ischaemia time, baseline disease and

immunosuppressive drugs may play a relevant role in the alteration of the intestinal barrier.[35,36]

Intestinal microflora as a cause of inflammation in chronic kidney disease

In CKD, the decreased clearance of proinflammatory cytokines, is associated with the development of oxidative stress and inflammation. The later are contributing factors to the progression of the disease and its complications, including cardiovascular disease, cachexia, and anaemia. Oxidative stress and chronic inflammation stimulate the NF-κB transcription factor, which is the key regulator of proinflammatory cytokines and chemokines. Increased permeability of intestinal barriers in CKD patients favours the translocation of bacterial products of intestinal origin, as evidenced by the presence of DNA fragments of circulating intestinal pathogens (aerobic and anaerobic), both in patients in different stages of CKD and on renal replacement therapy.[37–39] The increase in circulating bacterial products of intestinal origin activates innate immunity, promotes the inflammatory state associated with CKD and, increases the incidence of cardiovascular disease and mortality.[40–42]

Microbiota and uraemic toxins derived from the intestine in chronic kidney disease

Intestinal production of uraemic toxins

The origin of uraemic toxins in CKD is multiple. The importance of toxins generated by intestinal microbial metabolism[43] is increasingly recognised. Approximately 10 g of proteins reach the colon daily, where they are degraded by intestinal bacteria to metabolites such as ammonium, amines, thiols, phenols and indoles. These colon fermentation products are eliminated through faeces, although a portion is absorbed and eliminated by the kidney, so these are accumulated in CKD.[44] In CKD, the uraemic toxins derived from intestinal microflora are:

Phenols and indoles: p-cresol and indoxyl sulfate. Phenols include p-cresol, p-cresyl sulfate (PCS), p-cresyl glucuronide, phenylacetic acid, phenyl sulfate and phenol.[45]

- *p-Cresol/p-cresyl sulfate*: products of phenylalanine and tyrosine metabolism of intestinal anaerobic bacteria. p-Cresol is conjugated in the intestinal wall to PCS and p-cresyl glucuronide in the liver. PCS is the main circulating metabolite of p-cresol.[46]
- *Phenol*: mainly derives from ingestion, from the catabolism of tyrosine by intestinal bacteria, as well as from tobacco consumption.
- *Phenylacetic acid*: is the result of the degradation of phenylalanine.

Among the *indoles* are indoxyl sulfate (IS) and indoleacetic acid.[45] Both originate from the degradation of tryptophan by intestinal bacteria and are subsequently sulfated in the liver into IS. Indoles and phenols are uraemic toxins bound to proteins.[47]

Amines and polyamines: amines and polyamines are generated from intestinal microbial metabolism. An amino acid that is clinically relevant and of growing interest is trimethylamine N-oxide (TMAO). TMAO is produced by the intestinal metabolism of quaternary amines, such as choline/phosphatidylcholine, betaine, or L-carnitine. L-Carnitine, which is present in red meat, also induces the formation of TMAO and it is associated with an increase in cardiovascular disease.[48] Dietary sources of TMAO are red meats, meats in general, egg yolks, liver, dairy products and saltwater fish. In CKD, TMAO accumulates and its levels depends on the glomerular filtration, but its binding to proteins is low, and it is well eliminated with dialysis.

Polyamines are organic cations including cadaverine, spermine, spermidine and putrescine. They come from the decarboxylation of L-arginine, L-ornithine or lysine in the intestine. In CKD patients, putrescine, spermidine, and spermine are increased in serum.[49] These molecules have been shown to interact with insulin and lipoproteins, and contribute to the acceleration of atherosclerosis along with other factors such as hypertriglyceridemia.[50]

Biological and clinical consequences of the accumulation of uraemic toxins

The aforementioned uraemic toxins have been associated with deleterious biological effects in different tissues and cell lines[51,52] (Table 3), and with an increased risk of the progression of CKD, morbidity and mortality.

a) *Progression of CKD*: both IS and PCS are associated to the development of fibrosis, deterioration of renal function and disease progression.[52,53] In vitro studies have shown a deleterious effects of these molecules on renal tubular cells.[54] In a prospective study in patients with stage 1–5 CKD, the predictive role of both molecules in disease progression was confirmed.[55] In experimental animals, a diet rich in choline or TMAO preduces progressive tubulointerstitial fibrosis and renal dysfunction.[56]
b) *Cardiovascular complications*: in CKD patients, IS is associated with endothelial damage, arterial stiffness and aortic calcification[57]; and, in hemodialysis patients it is associated with atherosclerosis[58] and endothelial dysfunction,[59] it has a cardiac profibrotic effect, favours hypertrophy of myocardiocytes[60] and it is a predisposing factor of atrial fibrillation.[61] Similar vascular effects have been described with,[62] which is a predictor of cardiovascular risk in CKD patients.[63,64] In hemodialysis patients PCS and IS have been associated with peripheral vascular disease and thrombosis of vascular access.[65] A recent meta-analysis confirms the relationship of these molecules to cardiovascular risk in CKD.[66]

   Likewise, indoleacetic acid is associated with oxidative stress and inflammation markers, and it is a predictor of mortality and cardiovascular events in CKD.[67]

   Elevated levels of TMAO predicts coronary atherosclerotic burden[56] and mortality in patients with CKD,[68,69] although this is not shown in all reports.[70]
c) *Anaemia*: IS has been associated with anaemia of the renal patient; it interfere with the adequate production of erythropoietin[71,72] and increased eryptosis (programmed cell death of red blood cells).[73] Polyamines are associated

Table 3 – Effects of different uraemic toxins at the cellular and tissue level.

Organ/tissue	Toxin	Effect
Endothelium	IS	Increased senescence
		Induction of ROS and decrease in NO production
	IS and PCS	Increased expression of ICAM-1, MCP-1 and tissue factor
		Increased adhesion of leukocytes to the endothelium
	PCS	Inhibition of proliferation, viability, and repair
	IAA	Increased release of endothelial microparticles
		Increased endothelial permeability
		Increased ROS and inflammation and tissue factor expression
		Apoptosis of endothelial cell progenitors
Vascular smooth muscle fibre	IS	Increased proliferation
		Increased production of tissue factor
	PAA	Increased ROS and expression of osteoblastic proteins
		Increased ROS production
Vessels	IS	Increased aortic calcification and stiffness, expression of osteoblastic markers and OAT
	IS and PCS	Increased cellular senescence
	TMAO	Increased rolling and adhesion of leukocytes to the vessel
		Accelerated atherosclerosis
Leukocytes	PCS	Activation of the oxidative burst
	IS	Increased adhesion to the endothelium
	IS and IAA	Increased expression of mononuclear cell tissue factor
	TMAO	Increased expression of scavenger receptors in macrophages
Cardiac cells	IS	Hypertrophy of cardiomyocytes, production of collagen by myofibroblasts and inflammation
Heart	IS	Myocardial hypertrophy, cardiac fibrosis and oxidative stress
Renal tubular cells	PCS and IS	Activation of RAS, mesenchymal epithelial transition, and fibrosis
		Increased expression of proinflammatory genes and cytokines
	PCS	Increased methylation of the klotho gene and fibrosis
	IS	Increased tubular damage
	IS and IAA	Increased expression of MCP-1, ICAM-1, TGF-β and Smad3
		Increased oxidative stress, inhibition of proliferation, increased expression of PAI-1 and NF-κB activation
	PCS, IS, IAA	Decreased cell viability
Kidneys	IS	Increased fibrosis and angiotensinogen expression
		Decreased klotho expression and increased senescence
	IAA	Increased glomerulosclerosis
	TMAO	Increased monocyte infiltration
		Increased glomerular sclerosis and interstitial fibrosis
		Increased tubulointerstitial fibrosis and collagen deposition
Adipocytes	PCS and IS	Increased insulin resistance
Osteoclasts	IS	Alteration of differentiation and function
Osteoblasts	PCS and IS	Decreased cell viability and cell proliferation and increased ROS production
	IS	Decreases PTH receptor expression
		Promotes apoptosis
	PAA	Inhibits proliferation and differentiation

Source: Modified and extended from Biagi et al.[17]
PAA, phenylacetic acid; IAA, indole acetic acid; IS, indoxyl sulfate; OAT, organic acid transporters; PC, p-cresol; PCS, p-cresyl sulfate; PTH, parathyroid hormone; RAS, renin–angiotensin system; ROS, oxygen free radicals; TMAO, trimethylamine N-oxide.

to anaemia in renal patients, through an intra-erythrocytic effect,[74] reduces erythropoiesis, and inhibit the activity of erythropoietin.

d) *Alterations of bone-mineral metabolism*: IS reduces bone formation by promoting oxidative stress in osteoblasts and inducing resistance to PTH, which favours the development adynamic bone.[75] There is a positive correlation between FGF-23 and IS serum levels, suggesting an association between this molecule and metabolic bone disease in uraemic patients.[76] Likewise, less bone remodelling has been observed in uraemic rats with higher IS after a parathyroidectomy.[77]

e) *Insulin resistance*: In CKD patients the catabolism of insulin is reduced and often, they also have insulin resistance, which is associated with an increased risk of mortality; it seems that insulin resistance is related to some of the uraemic toxins.[78]

Prevention and treatment of dysbiosis

In recent years there is a growing interest in restoring the symbiosis of intestinal microflora in CKD aiming to reduce the generation of uraemic toxins, oxidative stress, and inflammation.[79]

a) *High fibre diet*: a high fibre diet increases the production of SCFA, which provides energy to the intestinal flora and allows amino acids that reach the colon to be incorporated into bacterial proteins and be excreted instead of being fermented into uraemic solutes. In addition, SCFAs are used as substrate by the intestinal mucosa helping to maintain their functionality and integrity. Fibre increases intestinal transit reducing the time for fermentation of amino acids and improves the composition of microflora which reduces the production of undesirable solutes. In CKD patients, there is a direct relationship between dietary protein/fibre ratio and PCS and IS levels, so a diet with a low protein/fibre ratio should be beneficial.[80] In healthy subjects, a vegetarian diet, as compared with the omnivore diet, reduces the generation IS or PCS; this effect was related to the higher fibre and lower protein content of the vegetarian diet.[81] A very low protein diet (0.3 g/kg body weight/day) supplemented with amino acid keto-analogues also reduces IS levels in patients with CKD.[82]

Several therapeutic interventions have recently explored to improve the dysbiosis of the intestinal microflora, reduce the absorption of uraemic toxins and the passage of endotoxins from the intestinal lumen.

b) *Prebiotics, probiotics, and symbiotics*: the generation of uraemic toxins could be reduced by selectively increasing saccharolyticbacteria (which digest dietary fibre) and decreasing proteolytic bacteria (protein and amino acid fermenters) in the colon. The main regulator of metabolism of colon bacteria is the availability of nutrients and specifically the rate of fermentable carbohydrates vs. nitrogen.

Prebiotics are non-digestible food components which, through selective fermentation, allow for specific changes in the composition or activity in gastrointestinal microflora, which are beneficial to the health and well-being of the host. Prebiotics stimulate the growth or activity of one or a limited number of bacteria in the colon; they may increase carbohydrate fermentables vs. nitrogen; they include inulin, fructooligosaccharides, galactooligosaccharides, etc. Inulin enriched with oligofructose reduces the generation of PCS and the serum concentrations in hemodialysis patients, but has no effect on IS.[83] Resistant starch reduces IS levels in hemodialysis patients and reduces PCS but not significantly.[84] In a CKD rat model, a diet rich in resistant starch delayed the progression of CKD and attenuated oxidative stress and inflammation.[85] Currently, a randomised, crossover, double-blind, phase 2 clinical trial in patients with stage

Table 4 – Clinical studies with probiotics in patients with CKD and their effects.

Author and year	Probiotic	Type of study	Results
Hida et al., 1996[88]	Lebenin	Observational, patients in HD ($n=25$), 4 weeks	↓ Indicate in faeces and serum ↓ p-Cresol in faeces
Simenhoff et al., 1996[89]	*Lactobacillus acidophilus*	Observational, patients in HD ($n=8$)	↓ Dimethylamine ↓ Nitrosodimethylamine
Takayama et al., 2003[90]	*Bifidobacterium longum* JCM008	Non-randomised, placebo-controlled. Patients in HD ($n=22$), 5 weeks	↓ Indoxyl sulfate
Ando et al., 2003[91]	*Bifidobacterium longum*	Observational, patients with CKD ($n=27$), 6 months	Reduction of the progression of CKD in patients with con Cr ≥4 mg/dl or P ≥ 4 mg/dl
Taki et al., 2005[92]	*Bifidobacterium longum*	Non-randomised, placebo-controlled. Patients in HD ($n=27$), 12 weeks	↓ Indoxyl sulfate, homocysteine and triglycerides
Ranganathan et al., 2009[93]	*Lactobacillus acidophilus* KB31, *Streptococcus thermophilus* KB27, *Bifidobacterium longum* KB35	Randomised, double-blind, crossover, placebo-controlled. Patients with CKD 3–4 ($n=16$), 6 months	BUN Uric acid ↑ Quality of life
Ranganathan et al., 2010[94]	*Lactobacillus acidophilus* KB31, *Streptococcus thermophilus* KB27, *Bifidobacterium longum* KB35	Multicentre, randomised, double-blind, placebo-controlled. Patients with CKD 3–4 ($n=46$), 6 months	BUN ↑ Quality of life Insurance
Miranda Alatriste et al., 2014[95]	*Lactobacillus casei shirota*	Randomised, placebo-controlled, patients with CKD 3–4 ($n=30$), 8 weeks	↓ Urea
Wang et al., 2015[96]	*Bifidobacterium bifidum* A218, *Bifidobacterium catenulatum* A302, *Bifidobacterium longum* A101, *Lactobacillus plantarum* A87	Randomised, double-blind, placebo-controlled, patients in PD ($n=39$), 6 months	↓ TNF-α, IL-5, IL-6 and endotoxin ↑ IL-10 Residual preservation of kidney function
Natarajan et al., 2014[97]	Renadyl	Randomised, double-blind, placebo-controlled, patients in HD ($n=22$), 8 weeks	No changes in quality of life Tendency towards reduction of indoxyl glucuronide, CRP and leucocyte count

Cr, creatinine; PD, peritoneal dialysis; CKD, chronic kidney disease; HD, haemodialysis; IL, interleukin; P, phosphorus; CRP, C-reactive protein.

3b-4 CKD is examining the effect of the supplementation of arabinoxylan-oligosaccharides on plasma levels of PCS and indole derivatives urinary excretion of these compounds and insulin resistance are also examined.[86]

Probiotics are defined as "living micro-organisms" that, being administered in adequate amounts, provide a health benefit to the host. A recent review evaluates the potential benefits of probiotics in general and especially in CKD.[87] The efficacy of probiotics to decrease levels of uraemic toxins and to delay the progression of CKD has been investigated in in vitro models, animal models and in patients with CKD. However, to date, there are no large-scale quality intervention studies and studies on clinical events to support their widespread use. There are only small studies, most of which,[88,92–95] but not all,[97] observe a decrease in uraemic toxin levels. Administration of *Bifidobacterium longum* in enteric capsules to patients with CKD had minimal effects on the progression of the disease in patients with CKD.[91] However, a randomised, double-blind trial in patients on peritoneal dialysis observed a significant reduction in serum proinflammatory endotoxin and cytokine levels, an increase in serum IL-10 levels, and the preservation of residual renal function after 6 months of treatment with a probiotic[96] (Table 4).

Symbiotics are probiotic supplements combined with prebiotics. In hemodialysis patients, on treatment with a symbiotic there is a decrease in the level of PCS, but not those of IS,[98] which was confirmed in another study.[102] Another study observed a delay in the progression of CKD with symbiotic treatment,[100] while another study did not observe a significant improvement in inflammation markers.[103] Finally, a randomised, double-blind, crossover study in patients with CKD[104] demonstrated a reduction in PCS levels, a non-significant decrease in IS and an increase in bifidobacteria and reduction of faecal ruminococcus, but no change in inflammation markers, oxidative stress, or endotoxins, although a slight increase in albuminuria was observed (Table 5).

One of the major limitations of probiotic or symbiotic therapy is that no study has yet demonstrated the sustained survival of probiotics in the dysbiotic colon of patients with CKD. There are also no studies that have evaluated the effect of these treatments on the levels of TMAO in this population. In choosing probiotics, the contribution of urease-containing bacteria must be considered, since they may increase intestinal ammonia generation, which may damage

Table 5 – Clinical studies with symbiotics in patients with CKD and their effects.

Author and year	Symbiotic	Study	Results
Nakabayashi et al., 2010[98]	*Lactobacillus casei shirota*, *Bifidobacterium breve yakult* and galactooligosaccharides	Observational, patients in HD ($n=9$), 4 weeks	↓ p-Cresol in plasma Normalisation of bowel habits Association of p-cresol and constipation
Ogawa et al., 2012[99]	*Bifidobacterium longum* JBL01 and oligosaccharides	Observational, patients in HD ($n=15$). Control group patients in HD ($n=16$), 4 weeks	↓ P levels that returned to baseline 2 weeks later
Pavan et al., 2014[100]	Probiotic and prebiotic	Prospective, open, randomised, placebo-controlled. Patients with CKD 3–5 ($n=24$), 12 months	Reduction in the progression of CKD
Cruz-Mora et al., 2014[101]	*Lactobacillus acidophilus*, *Bifidobacterium lactis* and inulin	Double-blind, randomised, placebo-controlled. Patients in HD ($n=18$), 2 months	↑ Bifidobacteria in faeces ↓ *Lactobacilli* in faeces (in the 2 groups) Improvements of GI symptoms
Guida et al., 2014[102]	*Lactobacillus plantarum*, *Lactobacillus casei* subsp. *Rhamnosus*, *Lactobacillus gasseri*, *Bifidobacterium infantis*, *Bifidobacterium longum*, *Lactobacillus acidophilus*, *Lactobacillus salivarius*, *Lactobacillus sporogenes* and *Streptococcus thermophilus* inulin and resistant tapioca starch	Randomised, double-blind, placebo-controlled. Patients with CKD 3–4 ($n=30$), 4 weeks	↓ p-Cresol in plasma With no changes in GI symptoms
Viramontes-Hörner et al., 2015[103]	*Lactobacillus acidophilus* and *Bifidobacterium lactis* + prebiotic (inulin)	Randomised, double-blind, placebo-controlled. Patients in HD ($n=42$), 2 months	Tendency to diminish levels of CRP and TNF-α. Improvement of GI symptoms
Rossi et al., 2014[104]	*Lactobacillus*, bifidobacteria and *Streptococcus* generates + inulin, fructooligosaccharides and galactooligosaccharides	Randomised, double-blind, crossover, placebo-controlled. Patients with CKD 4–5, 6 weeks with a washout of 4 weeks	Decreased PCS, decreased NS of IS Increased bifidobacteria and decreased ruminococcaceae in faeces. No changes in oxidative stress or inflammation markers and slight increase in albuminuria

CRD, chronic kidney disease; GI, gastrointestinal; HD, haemodialysis; NO, nonsignificant; P, phosphorus; CRP, C-reactive protein; PCS, p-cresyl sulfate.

epithelial tight junctions, and increase intestinal permeability to the passage of endotoxins from the intestinal lumen.[33,34]

c) *Adsorptive therapies*: the use of oral sorbents could decrease uraemic toxins and circulating intestinal endotoxins. AST-120 oral sorbents decrease IS levels in a dose-dependent manner.[105] In addition, a reduction in the IS, PCS, or phenyl sulfate and oxidative stress levels have been described in patients on haemodialysis.[106] Other authors have reported that the administration of AST-120 improves the erythropoietic response to CERA.[107] AST-120 improves intestinal barrier dysfunction and decreases endotoxin plasma levels, inflammation markers and oxidative stress in a CKD model in rats.[108]

Although small randomised, controlled studies in experimental animals and retrospective studies in patients have indicated a nephroprotective effect of AST-120 (reviewed by Schulman et al.[109]), a subsequent large randomised, controlled trial in patients with CKD was unable to confirm this.[109] The study had some methodological limitations, but also suggested the possibility that the objective of treating specific uraemic toxins may not be sufficient. However, another retrospective study of the long-term effects of AST-120 on patients with stage 3–5 CKD showed a reduction in the risk of progression to dialysis, mortality, cardiac events and vascular accident vs. those patients who did not receive it.[110]

Although a beneficial effect of sevelamer on IS and PCS has been described in in vitro studies, in vivo studies in mice or patients have not demonstrated a reduction in the levels of these uraemic toxins.[111] However, sevelamer does reduce endotoxin levels and systemic inflammation in patients on haemodialysis.[112,113]

Key concepts

1. In CKD, there is a dysbiosis of the intestinal microflora.
2. Intestinal microflora generate uraemic toxins that are absorbed and accumulate in CKD, and are associated with increased oxidative stress and inflammation.
3. In CKD, there is an increase in the permeability of the intestinal barrier that allows the passage into the systemic circulation of endotoxins and other bacterial products that aggravate the inflammatory state of CKD.
4. Changes in diet composition could improve microflora dysbiosis in CKD, reduce uraemic toxin levels, or restore intestinal mucosal permeability in CKD patients.
5. The use of probiotics, prebiotics or symbiotics opens an alternative in the treatment of intestinal dysbiosis associated with CKD, and may play a role in slowing the progression of CKD and in preventing relevant associated complications such as mortality and cardiovascular risk.

Conflicts of interest

The authors have no conflicts of interest to declare.

Acknowledgements

This work was supported by grants from Fondo de Investigaciones Sanitarias (PI16/01298), Madrid Society of Nephrology and REDinREN.

REFERENCES

1. Palmer C, Bick EM, DiGulio DB, Relman DA, Brown PO. Development of the human infant intestinal microbiota. PLoS Biol. 2007;5:e177.
2. Tojo R, Suarez A, Clemente MG, de los Reyes Gavilán C, Margolles A, Gueimonde M, et al. Intestinal microbiota in health and disease: role of bifidobacteria in gut homeostasis. World J Gastroenterol. 2014;20:15163–76.
3. O'Hara AM, Shanahan F. The gut flora as a forgotten organ. EMBO Rep. 2006;7:688–93.
4. Hacquard S, Garrido-Oter R, Gonzalez A, Spaepen S, Ackermann G, Lebeis S, et al. Microbiota and host nutrition across plant and animal kingdoms. Cell Host Microbe. 2015;17:603–16.
5. Huttenhower C, Gevers D, Knight R, Abubucker S, Badger JH, on behalf of the Human Microbiome Project Consortium. Structure, function and diversity of the healthy human microbiome. Nature. 2013;486:207–14.
6. Gevers D, Knight R, Petrosino JF, Huang K, McGuire AL, Birren BW, et al. The human microbiome project: a community resource for the healthy human microbiome. PLoS Biol. 2012;10:e1001377.
7. Meropol SB, Edwards A. Development of the infant intestinal microbiome: a bird's eye view of a complex process. Birth Defects Res. 2015;105:228–39.
8. Marques TM, Wall R, Ross RP, Fitzgerald GF, Ryan CA, Stanton C. Programming infant gut microbiota: influence of dietary and environmental factors. Curr Opin Biotechnol. 2010;21:149–56.
9. Scholtens PA, Oozeer R, Martin R, Amor KB, Kno J. The early settlers: intestinal micro-biology in early life. Annu Rev Food Sci Technol. 2012;3:425–47.
10. Koenig JE, Spor A, Scalfone N, Fricker AD, Stombaugh J, Knight R, et al. Succession of microbial consortia in the developing infant gut microbiome. Proc Natl Acad Sci U S A. 2011;108 Suppl. 1:4578–85.
11. Rajilic-Stojanovic M, Heilig HG, Molenaar D, Kajander K, Surakka A, Smidt H, et al. Development and application of the human intestinal tract chip, a phylogenetic microarray: analysis of universally conserved phylotypes in the abundant microbiota of young and elderly adults. Environ Microbiol. 2009;11:1736–51.
12. Ottman N, Smidt H, de Vos WM, Belzer C. The function of our microbiota: who is out there and what they do? Front Cell Infect Microbiol. 2012;2:104.
13. Arumugam M, Raes J, Pelletier E, le Paslier D, Yamada T, Mende DR, et al. Enterotypes of the human gut microbiome. Nature. 2011;473:174–80.
14. Claesson MJ, Jeffery IB, Conde S, Power SE, O'Connor EM, Cusack S, et al. Gut microbiota composition correlates with diet and health in the elderly. Nature. 2012;488:178–84.
15. Suarez JE. Microbiota autóctona, probióticos y prebióticos. Nutr Hosp. 2015;31 Suppl. 1:3–9.
16. Chassard C, Lacroix C. Carbohydrates and the human microbiota. Curr Opin Clin Nutr Metab Care. 2013;16:453–60.
17. Biagi E, Nylund L, Candela M, Ostan R, Bucci L, Pini E, et al. Through ageing, and beyond: gut microbiota and

inflammatory status in seniors and centenarians. PLoS ONE. 2010;5:e10667.
18. Man AL, Bertelli E, Rentini S, Regoli M, Briars G, Marini M, et al. Age-associated modifications of intestinal permeability and innate immunity in human small intestine. Clin Sci (Lond). 2015;129:515–27.
19. Soenen S, Rayner CK, Jones KL, Horowitz M. The ageing gastrointestinal tract. Curr Opin Clin Metab Care. 2016;19:12–8.
20. Bischoff SC. Microbiota and aging. Curr Opin Clin Metab Care. 2016;19:26–30.
21. Quercia S, Candela M, Giuliani C, Turroni S, Luiselli D, Rampelli S, et al. From lifetime to evolution: timescales of human gut microbiota adaptation. Front Microbiol. 2014;5:587.
22. Cani PD, Everard A, Duparc T. Gut microbiota, enteroendocrine functions and metabolism. Curr Opin Pharmacol. 2013;13:935–40.
23. Hevia A, Delgado S, Sánchez B, Margolles A. Molecular players involved in the interaction between beneficial bacteria and the immune system. Front Microbiol. 2015;6:1285.
24. Aron-Wisnewsky JA, Clement K. The gut microbiome, diet, and links to cardiometabolic and chronic disorders. Nat Rev Nephrol. 2016;12:169–81, http://dx.doi.org/10.1038/nrneph.2015.191. Epub 2015 Nov 30.
25. Mafra D, Lobo JC, Barros F, Koppe L, DVarizi N, Fouque D. Role of altered intestinal microbiota in systemic inflammation and cardiovascular disease in chronic kidney disease. Future Microbiol. 2014;9:399–410.
26. Sabatino A, Regolisti G, Brusasco I, Cabassi A, Morabito S, Fiaccadori E. Alterations of intestinal barrier and microbiota in chronic kidney disease. Nephrol Dial Transplant. 2015;30:924–33.
27. Anders HJ, Andersen K, Stecher B. The intestinal microbiota, a leaky gut, and abnormal immunity in kidney disease. Kidney Int. 2013;83:1010–6.
28. Jemberg C, Löfmark S, Edlund C, Jansson JK. Long-term impact of antibiotic exposure on the human intestinal microbiota. Microbiology. 2010;156:3216–23.
29. Jakobsson HE, Jemberg C, Andersson AF, Sjölund-Karlsson M, Jansson JK, Engstrand L. Short-term antibiotic treatment has differing long-term impacts on the human throat and gut microbiome. PLoS ONE. 2010;5:e9836.
30. Wu MJ, Chang CS, Cheng CH, Chen CH, Lee WC, Hsu YH, et al. Colonic transit time in long-term dialysis patients. Am J Kidney Dis. 2004;44:322–7.
31. Kortman GA, Raffatellu M, Swinkels DW, Tjalsma H. Nutritional iron turned inside out: intestinal stress from a gut microbial perspective. FEMS Microbiol Rev. 2014;38:1202–34.
32. Weiss G. Dietary iron supplementation: a proinflammatory attack on the intestine? Gut. 2015;64:696–7.
33. Vaziri ND. CKD impairs barrier function and alters microbial flora of the intestine: a major link to inflammation and uremic toxicity. Curr Opin Nephrol Hypertens. 2012;21:587–92.
34. Goncalves S, Pecoits-Filho R, Perreto S, Barberato SH, Stinghen AE, Lima EG, et al. Associations between renal function, volume status and endotoxemia in chronic kidney disease patients. Nephrol Dial Transpl. 2006;21:2178–794.
35. Alegre ML, Mannon RB, Mannon PJ. Thee microbiota, the immune system and the allograft. Am J Transplant. 2014;14:1236–48.
36. Bromberg JS, Fricke WF, Brinkman CC, Simon T, Mongodin EF. Microbiota – implications for immunity and transplantation. Nat Rev Nephrol. 2015;11:342–53.
37. Shi K, Wang F, Jiang H, Liu H, Wei M, Wang Z, et al. Gut bacterial translocation may aggravate microinflammation in hemodialysis patients. Dig Dis Sci. 2014;59:2109–17.
38. Wang F, Jiang H, Shi K, Ren Y, Zhan P, Cheng S. Gut bacterial translocation is associated with microinflammation in end-stage renal disease patients. Nephrology (Carlton). 2012;17:733–8.
39. Mafra D, Fouque D. Gut microbiota and inflammation in chronic kidney disease patients. Clin Kidney J. 2015;8:332–4.
40. McIntyre CW, Harrison LE, Eldehni MT, Jefferies HJ, Szeto CC, John SG, et al. Circulating endotoxemia: a novel factor in systemic inflammation and cardiovascular disease in chronic kidney disease. Clin J Am Soc Nephrol. 2011;6:133–41.
41. Vanholder R, Glorieux G. The intestine and the kidneys: a bad marriage can be hazardous. Clin Kidney J. 2015:168–79.
42. Ramenazani A, Massy ZA, Meijers B, Evenepoel P, Vanholder R, Raj DS. The gut microbiome in uremia: potential therapeutic target. Am J Kidney Dis. 2016;67:483–98, http://dx.doi.org/10.1053/j.ajkd.2015.09.027. Epub 2015 Nov 15.
43. Wikoff WR, Anfora AT, Liu J, Schultz PG, Lesley SA, Peters EC, et al. Metabolomics analysis reveals large effects of gut microflora on mammalian blood metabolites. Proc Natl Acad Sci U S A. 2009;106:3698–703.
44. Evenepoel P, Meijers BK, Bammens BR, Verbeke K. Uremic toxins originating from colonic microbial metabolism. Kidney Int Suppl. 2009:S12–9.
45. Jourde-Chiche N, Dou L, Cerini C, Dignat-George F, Vanholder R, Brunet P. Protein-bound toxins – update. Semin Dial. 2009;22:334–9.
46. Martinez AW, Recht NS, Hostetter TH, Meyer TW. Removal of P-cresol sulfate by hemodialysis. J Am Soc Nephrol. 2005;16:3430–6.
47. Vanholder R, de Smet R, Glorieux G, Argilés A, Baurmeister U, Brunet P, et al., European Uremic Toxin Work Group (EUTox). Review on uremic toxins: classification, concentration, and interindividual variability. Kidney Int. 2003;63:1934–43.
48. Koeth RA, Wang Z, Levison BS, Buffa JA, Org E, Sheehy BT, et al. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. Nat Med. 2013;19:576–85.
49. Saito A, Takagi T, Chung TG, Ohta K. Serum levels of polyamines in patients with chronic renal failure. Kidney Int. 1983;24 Suppl. 62:S2–4.
50. Lutz W. A uremic peptide containing polyamine: formation and possible role in uremic hypertriglyceridemia. Physiol Chem Phys. 1980;12:451–6.
51. Vanholder R, Schepers E, Pletinck A, Nagler EV, Glorieux G. The uremic toxicity of indoxyl sulfate and p-cresyl sulfate: a systematic review. J Am Soc Nephrol. 2014;25:1897–907.
52. Mutsaers HA, Stribos EG, Glorieux G, Vanholder R, Olinga P. Chronic kidney disease and fibrosis: the role of uremic retention solutes. Front Med (Lausanne). 2015.
53. Meijers BK, Evenepoel P. The gut-kidney axis: indoxyl sulfate, p-cresyl sulfate and CKD progression. Nephrol Dial Transplant. 2011;26:759–61.
54. Motojima M, Hosokawa A, Yamato H, Muraki T, Yoshioka T. Uremic toxins of organic anions up-regulate PAI-1 expression by induction of NF-kappaB and free radical in proximal tubular cells. Kidney Int. 2003;63:1671–80.
55. Wu IW, Hsu KH, Lee CC, Sun CY, Hsu HJ, Tsai CJ, et al. p-Cresyl sulphate and indoxyl sulphate predict progression of chronic kidney disease. Nephrol Dial Transplant. 2011;26:938–47.
56. Stubbs JR, House JA, Ocque AJ, Zhang S, Johnson C, Kimber C, et al. Serum trimethylamine-N-oxide is elevated in CKD

and correlates with coronary atherosclerosis burden. J Am Soc Nephrol. 2016;27:305–13, http://dx.doi.org/10.1681/ASN.2014111063. Epub 2015 Jul 30.
57. Barreto FC, Barreto DV, Liabeuf S, Meert N, Glorieux G, Temmar M, et al., European Uremic Toxin Work Group (EUTox). Serum indoxyl sulfate is associated with vascular disease and mortality in chronic kidney disease patients. Clin J Am Soc Nephrol. 2009;4:1551–8.
58. Raff AC, Meyer TW, Hostetter TH. New insights into uremic toxicity. Curr Opin Nephrol Hypertens. 2008;17:560–5.
59. Faure V, Dou L, Sabatier F, Cerini C, Sampol J, Berland Y, et al. Elevation of circulating endothelial microparticles in patients with chronic renal failure. J Thromb Haemost. 2006;4:566–73.
60. Lekawanvijit S, Adrahtas A, Kelly DJ, Kompa AR, Wang BH, Krum H. Does indoxyl sulfate, a uraemic toxin, have direct effects on cardiac fibroblasts and myocytes? Eur Heart J. 2010;31:1771–9.
61. Aoki K, Teshima Y, Kondo H, Saito S, Fukui A, Fukunaga N, et al. Role of indoxyl sulfate as a predisposing factor for atrial fibrillation in renal dysfunction. J Am Heart Assoc. 2015;4:e002023.
62. Gross P, Massy ZA, Henaut L, Boudot C, Cagnard J, March C, et al. Para-cresyl sulfate acutely impairs vascular reactivity and induces vascular remodeling. J Cell Physiol. 2015;230:2927–35.
63. Poesen R, Viaene L, Verbeke K, Augustijns P, Bammens B, Claes K, et al. Cardiovascular disease relates to intestinal uptake of p-cresol in patients with chronic kidney disease. BMC Nephrol. 2014;9:87.
64. Meijers BK, Bammens B, de Moor B, Verbeke K, Vanrenterghem Y, Evenepoel P. Free p-cresol is associated with cardiovascular disease in hemodialysis patients. Kidney Int. 2008;73:1174–80.
65. Lin CJ, Pan CF, Liu HL, Chuang CK, Jayakumar T, Wang TJ, et al. The role of protein-bound uremic toxins on peripheral artery disease and vascular access failure in patients on hemodialysis. Atherosclerosis. 2012;225:173–9.
66. Lin CJ, Wu V, Wu PC, Wu CJ. Meta-analysis of the associations of p-cresyl sulfate (PCS) and indoxyl sulfate (IS) with cardiovascular events and all-cause mortality in patients with chronic renal failure. PLOS ONE. 2015;10:e0132589.
67. Dou L, Sallée M, Cerini C, Poitevin S, Gondouin B, Jourde-Chiche N, et al. The cardiovascular effect of the uremic solute indole-3 acetic acid. J Am Soc Nephrol. 2015;26:876–87.
68. Tang WH, Wang Z, Kennedy DJ, Wu Y, Buffa JA, Agatisa-Boyle B, et al. Gut microbiota-dependent trimethylamine N-oxide (TMAO) pathway contributes to both development of renal insufficiency and mortality risk in chronic kidney disease. Circ Res. 2015;116:448–55.
69. Missailidis C, Hällqvist J, Qureshi AR, Barany P, Heimbürger O, Lindholm B, et al. Serum trimethylamine-N-oxide is strongly related to renal function and predicts outcome in chronic kidney disease. PLOS ONE. 2016;11:e0141738.
70. Kaysen GA, Johansen KL, Chertow GM, Dalrymple LS, Kornak J, Grimes B, et al. Associations of trimethylamine N-oxide with nutritional and inflammatory biomarkers and cardiovascular outcomes in patients new to dialysis. J Ren Nutr. 2015;25:351–6.
71. Chiang CK, Tanaka T, Inagi R, Fujita T, Nangaku M. Indoxyl sulfate, a representative uremic toxin, suppresses erythropoietin production in a HIF-dependent manner. Lab Invest. 2011;91:1564–71.
72. Nangaku M, Mimura I, Yamaguchi J, Higashijima Y, Wada T, Tanaka T. Role of uremic toxins in erythropoiesis-stimulating agent resistance in chronic kidney disease and dialysis patients. J Ren Nutr. 2015;25:160–3.
73. Ahmed MS, Abed M, Voelkl J, Lang F. Triggering of suicidal erythrocyte death by uremic toxin indoxyl sulfate. BMC Nephrol. 2013;14:244.
74. Yoshida K, Yoneda T, Kimura S, Fujimoto K, Okajima E, Hirao Y. Polyamines as an inhibitor on erythropoiesis of hemodialysis patients by in vitro bioassay using the fetal mouse liver assay. Ther Apher Dial. 2006;10:267–72.
75. Nii-Kono T, Iwasaki Y, Uchida M, Fujieda A, Hosokawa A, Motojima M, et al. Indoxyl sulfate induces skeletal resistance to parathyroid hormone in cultured osteoblastic cells. Kidney Int. 2007;71:738–43.
76. Lin CJ, Pan CF, Chuang CK, Liu HL, Sun FJ, Wang TJ, et al. Association of indoxyl sulfate with fibroblast growth factor 23 in patients with advanced chronic kidney disease. Am J Med Sci. 2014;347:370–6.
77. Hirata J, Hirai K, Asai H, Matsumoto C, Inada M, Miyaura C, et al. Indoxyl sulfate exacerbates low bone turnover induced by parathyroidectomy in young adult rats. Bone. 2015;79:252–8.
78. Soulage CO, Koppe L, Fouque D. Protein-bound uremic toxins... new targets to prevent insulin resistance and dysmetabolism in patients with chronic kidney disease. J Ren Nutr. 2013;23:464–6.
79. Ramezani A, Raj DS. The gut microbiome, kidney disease, and targeted interventions. J Am Soc Nephrol. 2014;25:657–70.
80. Rossi M, Johnson DW, Xu H, Carrero JJ, Pascoe E, French C, et al. Dietary protein–fiber ratio associates with circulating levels of indoxyl sulfate and p-cresyl sulfate in chronic kidney disease patients. Nutr Metab Cardiovasc Dis. 2015;25:860–5.
81. Patel KP, Luo FJ, Plummer NS, Hostetter TH, Meyer TW. The production of p-cresol sulfate and indoxyl sulfate in vegetarians versus omnivores. Clin J Am Soc Nephrol. 2012;7:982–8.
82. Marzocco S, Dal Piaz F, Di Micco L, Torraca S, Sirico ML, Tartaglia D, et al. Very low protein diet reduces indoxyl sulfate levels in chronic kidney disease. Blood Purif. 2013;35:196–201.
83. Meijers BK, de Preter V, Verbeke K, Vanrenterghem Y, Evenepoel P. p-Cresyl sulfate serum concentrations in haemodialysis patients are reduced by the prebiotic oligofructose enriched inulin. Nephrol Dial Transplant. 2010;25:219–24.
84. Sirich TL, Plummer NS, Gardner CD, Hostetter TH, Meyer TW. Effect of increasing dietary fiber on plasma levels of colon-derived solutes in hemodialysis patients. Clin J Am Soc Nephrol. 2014;9:1603–10.
85. Vaziri ND, Liu SM, Lau WL, Khazaeli M, Nazertehrani S, Farzaneh SH, et al. High amylose resistant starch diet ameliorates oxidative stress, inflammation, and progression of chronic kidney disease. PLOS ONE. 2014;9:e114881.
86. The effect of arabinoxylan-oligosaccharides (AXOS) on intestinal generation of microbial metabolites in chronic kidney disease. Available from: https://clinicaltrials.gov/ct2/show/study/NCT02141815?term5Bj%C3%B6rn1Meijers&rank54 2015 [accessed 20.03.16].
87. Koppe L, Mafra D, Fouque D. Probiotics and chronic kidney disease. Kidney Int. 2015;88:958–66.
88. Hida M, Aiba Y, Sawamura S, Suzuki N, Satoh T, Koya Y. Inhibition of the accumulation of uremic toxins in the blood and their precursors in the feces after oral administration of Lebenin, a lactic acid bacteria preparation, to uremic patients undergoing hemodialysis. Nephron. 1996;74:349–55.
89. Simenhoff ML, Dunn SR, Zollner GP, Fitzpatrick ME, Emery SM, Sandine WE, et al. Biomodulation of the toxic and

nutritional effects of small bowel bacterial overgrowth in end-stage kidney disease using freeze-dried *Lactobacillus acidophilus*. Miner Electrolyte Metab. 1996;22:92–6.
90. Takayama F, Taki K, Niwa T. Bifidobacterium in gastro-resistant seamless capsule reduces serum levels of indoxyl sulfate in patients on hemodialysis. Am J Kidney Dis. 2003;41:S142–5.
91. Ando Y, Miyata Y, Tanba K, Saito O, Muto S, Kurosu M, et al. Effect of oral intake of an enteric capsule preparation containing *Bifidobacterium longum* on the progression of chronic renal failure. Nihon Jinzo Gakkai Shi. 2003;45:759–64.
92. Taki K, Takayama F, Niwa T. Beneficial effects of Bifidobacteria in a gastroresistant seamless capsule on hyperhomocysteinemia in hemodialysis patients. J Ren Nutr. 2005;15:77–80.
93. Ranganathan N, Friedman EA, Tam P, Rao V, Ranganathan P, Dheer R. Probiotic dietary supplementation in patients with stage 3 and 4 chronic kidney disease: a 6-month pilot scale trial in Canada. Curr Med Res Opin. 2009;25:1919–30.
94. Ranganathan N, Ranganathan P, Friedman EA, Joseph A, Delano B, Goldfarb DS, et al. Pilot study of probiotic dietary supplementation for promoting healthy kidney function in patients with chronic kidney disease. Adv Ther. 2010;27:634–47.
95. Miranda Alatriste PV, Urbina Arronte R, Gómez Espinosa CO, Espinosa Cuevas MÁ. Effect of probiotics on human blood urea levels in patients with chronic renal failure. Nutr Hosp. 2014;29:582–90.
96. Wang I-K, Wu YY, Yang YF, Ting IW, Lin CC, Yen TH, et al. The effect of probiotics on serum levels of cytokine and endotoxin in peritoneal dialysis patients: a randomised, double-blind, placebo-controlled trial. Benef Microbes. 2015;6:423–30.
97. Natarajan R, Pechenyak B, Vyas U, Ranganathan P, Weinberg A, Liang P, et al. Randomized controlled trial of strain-specific probiotic fórmulation (Renadyl) in dialysis patients. Biomed Res Int. 2014;2014:568571.
98. Nakabayashi I, Nakamura M, Kawakami K, Ohta T, Kato I, Uchida K, et al. Effects of synbiotic treatment on serum level of p-cresol in haemodialysis patients: a preliminary study. Nephrol Dial Transplant. 2010;26:1094–8.
99. Ogawa T, Shimada M, Nagano N, Ito K, Ando T, Shimomura Y, et al. Oral administration of *Bifidobacterium longum* in a gastro-resistant seamless capsule decreases serum phosphate levels in patients receiving haemodialysis. Clin Kidney J. 2012;5:373–4.
100. Pavan M. Influence of prebiotic and probiotic supplementation on the progression of chronic kidney disease. Minerva Urol Nephrol. 2014.
101. Cruz-Mora J, Martínez-Hernández NE, Martín del Campo-López F, Viramontes-Hörner D, Vizmanos-Lamotte B, Muñoz-Valle JF, et al. Effects of a symbiotic on gut microbiota in Mexican patients with end-stage renal disease. J Ren Nutr. 2014;24:330–5.
102. Guida B, Germanò R, Trio R, Russo D, Memoli B, Grumetto L. Effect of short-term synbiotic treatment on plasma p-cresol levels in patients with chronic renal failure: a randomized clinical trial. Nutr Metab Cardiovasc Dis. 2014;24:1043–9.
103. Viramontes-Hörner D, Márquez-Sandoval F, Martín-del-Campo F, Vizmanos-Lamotte B, Sandoval-Rodríguez A, Armendáriz-Borunda J, et al. Effect of a symbiotic gel (*Lactobacillus acidophilus* + *Bifidobacterium lactis* + Inulin) on presence and severity of gastrointestinal symptoms in hemodialysis patients. J Ren Nutr. 2015;25:284–91.
104. Rossi M, Johnson DW, Morrison M, Pascoe EM, Coombes JS, Forbes JM, et al. Synbiotics Easing Renal Failure by Improving Gut Microbiology (SYNERGY): a randomised cross-over trial. Clin J Am Soc Nephrol. 2016;11:223–31.
105. Schulman G, Agarwal R, Acharya M, Berl T, Blumenthal S, Kopyt N. A multicenter, randomized, double-blind, placebo-controlled, dose-ranging study of AST-120 (Kremezin) in patients with moderate to severe CKD. Am J Kidney Dis. 2006;47:565–77.
106. Yamamoto S, Kazama JJ, Omori K, Matsuo K, Takahashi Y, Kawamura K, et al. Continuous reduction of protein-bound uraemic toxins with improved oxidative stress by using the oral charcoal adsorbent AST-120 in haemodialysis patients. Sci Rep. 2015;5:14381, http://dx.doi.org/10.1038/srep14381.
107. Wu IW, Hsu KH, Sun CY, Tsai CJ, Wu MS, Lee CC. Oral adsorbent AST-120 potentiates the effect of erythropoietin-stimulating agents on stage 5 chronic kidney disease patients: a randomized crossover study. Nephrol Dial Transplant. 2014;29:1719–27.
108. Vaziri ND, Yuan J, Khazaeli M, Masuda Y, Ichii H, Liu S. Oral activated charcoal adsorbent (AST-120) ameliorates chronic kidney disease-induced intestinal epithelial barrier disruption. Am J Nephrol. 2013;37:518–25.
109. Schulman G, Berl T, Beck GJ, Remuzzi G, Ritz E, Arita K, et al. Randomized placebo controlled EPPIC trials of AST-120 in CKD. J Am Soc Nephrol. 2015;26:1732–46.
110. Sato E, Tanaka A, Oyama JI, Yamasaki A, Shimomura M, Hiwatashi A, et al. Long-term effects of AST-120 on the progression and prognosis of pre-dialysis chronic kidney disease: a 5-year retrospective study. Heart Vessels. 2016;31:1625–32.
111. De Smet R, Thermote F, Lameire N. Sevelamer hydrochloride adsorbs the uremic compound indoxyl sulfate. J Am Soc Nephrol. 2003:208. ASN Renal Week. Abstract F-PO-660.
112. Stinghen AE, Gonçalves SM, Bucharles S, Branco FS, Gruber B, Hauser AB, et al. Sevelamer decreases systemic inflammation in parallel to a reduction in endotoxemia. Blood Purif. 2010;29:352–6.
113. Navarro-González JF, Mora-Fernández C, Muros de Fuentes M, Donate-Correa J, Cazaña-Pérez V, García-Pérez J. Effect of phosphate binders on serum inflammatory profile, soluble CD14, and endotoxin levels in hemodialysis patients. Clin J Am Soc Nephrol. 2011;6:2272–9.