

Nutrición Hospitalaria

Nutrición Hospitalaria

ISSN: 0212-1611

ISSN: 1699-5198

Grupo Arán

Stampini-Oliveira-Lopes, Rita-de-Cássia; Pereira-Balbino, Karla; de-Paula-Jorge, Mônica;
Queiroz-Ribeiro, Andréia; Stampini-Duarte-Martino, Hércia; Gonçalves-Alfenas, Rita-de-Cássia

Modulation of intestinal microbiota, control of nitrogen products and
inflammation by pre/probiotics in chronic kidney disease: a systematic review

Nutrición Hospitalaria, vol. 35, no. 3, 2018, May-June, pp. 722-730

Grupo Arán

DOI: <https://doi.org/10.20960/nh.1642>

Available in: <https://www.redalyc.org/articulo.oa?id=309258263032>

- How to cite
- Complete issue
- More information about this article
- Journal's webpage in redalyc.org

redalyc.org

Scientific Information System Redalyc

Network of Scientific Journals from Latin America and the Caribbean, Spain and
Portugal

Project academic non-profit, developed under the open access initiative



Nutrición Hospitalaria



Revisión

Modulation of intestinal microbiota, control of nitrogen products and inflammation by pre/probiotics in chronic kidney disease: a systematic review

Modulación de microbiota intestinal, control de productos de nitrógeno e inflamación por pre/probióticos en la enfermedad renal crónica: una revisión sistemática

Rita de Cássia Stampini Oliveira Lopes, Karla Pereira Balbino, Mônica de Paula Jorge, Andréia Queiroz Ribeiro, Hércia Stampini Duarte Martino and Rita de Cássia Gonçalves Alfenas

Department of Nutrition and Health. Federal University of Viçosa. Brazil

Abstract

Dysbiosis may favor the occurrence of inflammation and oxidative stress in chronic kidney disease (CKD). It has been suggested that the intake of pre/probiotics may control the progression of chronic kidney disease. Thus, the objective of this study was to systematically review the literature on the effects of pre/probiotic intake on the intestinal microbiota, control of nitrogen products, oxidative stress, and inflammation in CKD patients. The literature search was conducted on MEDLINE, LILACS, Cochrane Library of Clinical Trials, and Science Direct. After careful evaluation by the reviewers, ten potentially relevant articles were selected for this study. Based on previous studies, intake of prebiotics appears to have the following effects: increased bifidobacteria and lactobacillus counts; reduced formation of uremic toxin, p-cresol, and its serum concentrations; improved lipid profiles; reduced systemic inflammatory state and concentrations of oxidative stress markers. Similarly, consumption of probiotics can reduce blood urea and serum phosphate concentrations. Furthermore, an increase in fecal volume and intestinal *Bifidobacterium* and a reduction in p-cresol serum and blood urea concentrations were observed in response to symbiotic intake. These results suggest that consumption of pre/probiotics may modulate the intestinal microbiota, and promote the growth and metabolism of anaerobic bacteria by decreasing the production of uremic solutes, further causing oxidative stress and systemic inflammation in CKD patients.

Key words:

Hemodialysis.
Oxidative stress.
Symbiotic. Uremia.
Uremic toxins.

Resumen

La disbiosis puede favorecer la incidencia de inflamación y de estrés oxidativo en enfermedades renales crónicas. Se ha sugerido que el consumo de prebióticos y probióticos puede controlar la progresión de enfermedades renales crónicas. De este modo, el objetivo de este estudio es revisar sistemáticamente la literatura sobre los efectos del consumo de prebióticos y probióticos en la microbiota intestinal, el control de los productos de nitrógeno, el estrés oxidativo y la inflamación en enfermedades renales crónicas. La búsqueda bibliográfica fue realizada por medio de MEDLINE, LILACS, Cochrane Library of Clinical Trials y Science Direct. Diez artículos fueron incluidos en este estudio. Los prebióticos parecen aumentar las bifidobacterias y el recuento de lactobacillus, reducir la formación de toxina urémica, p-cresol y su concentración sérica; mejorar los perfiles lipídicos y reducir el estado de inflamación sistémica y la concentración de indicadores de estrés oxidativo. El consumo de probióticos puede reducir la urea en sangre y la concentración de fosfato sérico. Se verificó el aumento del volumen fecal y de las bifidobacterias intestinales y la reducción de la concentración sérica de p-cresol y de urea en sangre en respuesta a la ingesta de simbióticos. Estos resultados indican que los prebióticos y probióticos modulan la microbiota intestinal y promueven el crecimiento del metabolismo de bacterias anaerobias, disminuyendo la producción de solutos urémicos y la incidencia de estrés oxidativo e inflamación sistémica en pacientes portadores de enfermedades renales crónicas.

Palabras clave:

Hemodiálisis. Estrés oxidativo. Simbiótico. Uremia. Toxinas urémicas.

Received: 01/11/2017 • Accepted: 14/03/2018

Lopes RCSO, Balbino KP, Jorge MP, Ribeiro AQ, Martino HSD, Alfenas RCG. Modulation of intestinal microbiota, control of nitrogen products and inflammation by pre/probiotics in chronic kidney disease: a systematic review. Nutr Hosp 2018;35:722-730

DOI: <http://dx.doi.org/10.20960/nh.1642>

Correspondence:

Rita Cássia Stampini Oliveira Lopes. Department of Nutrition and Health. Federal University of Viçosa. Av. PH Rolfs, s/n. Viçosa, Minas Gerais. 36571-000 Brazil
e-mail: rita.lopes@ufv.br

INTRODUCTION

Chronic kidney disease (CKD) is a global public health problem. In countries, such as the United States of America and Australia, it affects 10-13% of the population (1,2). Over the last decade, there has been an increase in the incidence and prevalence of this disease, with a significant increase in the number of patients requiring dialysis therapy (3). Studies conducted in Brazil have shown a gradual increase in the prevalence of CKD, with a high proportion of patients in need of dialysis treatment. In 2016, 122.825 CKD patients were recorded to be on dialysis, and 92.3% of patients were on hemodialysis (HD) (4,5).

Uremia is a serious complication of CKD, and it is associated with renal injury, food restriction, and hydration status. Besides activating the renin-angiotensin-aldosterone system and favoring the occurrence of vascular calcifications, uremia also changes the microbiota (known as dysbiosis) and increases intestinal permeability (6-8). It results in an increased flow of urea into the intestinal lumen, which is then hydrolyzed by microbial urease. Bacterial urease catalyzes the hydrolysis of urea to produce ammonium hydroxide; this reaction leads to an increase in the local pH, facilitating the growth of pathogenic bacteria and promoting mucosal irritation and damage (9-10). These changes allow entry of endotoxins and other harmful luminal contents into the underlying tissues and systemic circulation, favoring the manifestation of other diseases (6,7,11,12).

Patients with CKD demonstrate significant quantitative and qualitative changes in intestinal microbiota, related to the overgrowth of aerobic and anaerobic pathogenic bacterial species (7,11). These bacteria can use nitrogen products, thus increasing the production of uremic toxins, such as indoxyl sulfate and p-cresyl sulfate. Such toxins induce inflammation, oxidative stress, and cause a pathophysiological impact, resulting in structural and functional changes that indirectly influence patient morbidity and mortality (13,14).

In uremic patients, oxidative stress and inflammation cause dysregulation of the immune system. This is evidenced by the presence of elevated oxidative biomarkers, such as lipid oxidation and protein oxidation products (15,16). A cross-sectional study involving patients with chronic renal failure demonstrated that the presence of indoxyl sulfate and p-cresyl sulfate was also associated with elevated concentrations of inflammatory markers and increased arterial stiffness, a key clinical finding associated with CKD (17). In the past decade, these toxins have been associated with the progression, cardiovascular morbidity and mortality of CKD patients (18). In addition to uremia and metabolic acidosis, routine therapeutic interventions for treating CKD, such as dietary restriction of fruits, vegetables, and foods with high fiber content, iron intake, phosphate binders, and antibiotics modify the colonic environment. These modifications negatively affect the intestinal microbiota and induce the production of uremic toxins and inflammatory markers (19).

Some interventions are being used to modulate the intestinal microbiota, block LPS or attenuate inflammation, or target adsorption of uremic toxin end products of microbial fermentation (20).

Previously published review articles have described some of these interventions: administration of small intestine alpha-glycosidase inhibitor that increases the fermentation of carbohydrates in the colon and can reduce the colonic generation of p-cresol; utilization of essential oils as agents to treat dysbiosis; use of oral adsorbents to restore epithelial tight-junction proteins and reduce plasma endotoxin and markers of oxidative stress and inflammation; administration of synthetic TLR4 antagonists to inhibit LPS signaling; ingestion of prebiotics and/or probiotics that play an important role in the progression of CKD (12,20).

The results of a recent study suggest that the ingestion of prebiotics and probiotics can increase the production of short chain fatty acids, modulating the intestinal microbiota (17). They can also reduce intestinal permeability via blocking the entry of endotoxins into the bloodstream and suppressing inflammation (21); these events are believed to play an important role in the progression of CKD. Therefore, the objective of this study was to systematically review the literature on the effects of intake of prebiotic and/or probiotic products on the intestinal microbiota, oxidative stress, and inflammation in patients with CKD.

METHODS

This systematic review was conducted according to a pre-specified protocol and is described according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (22). This article is based on previously conducted studies, and it does not include studies conducted by any of the authors of this study.

SEARCH STRATEGY

A literature review was conducted in computerized databases MEDLINE (PubMed), Latin American and Caribbean Health Sciences (LILACS), Cochrane Library of Clinical Trials and Science Direct. Databases were searched using the key words: "chronic kidney disease," "hemodialysis," "intestinal permeability," "intestinal/gut microbiota," "inflammation," "oxidative stress," "uremic toxins," "supplementation," "probiotic," "prebiotic," and "symbiotic." These terms were searched alone or in combinations with each other. The search was limited to articles published between 2005 and 2016.

First, a manual search on references of all selected articles was conducted. To ensure that no relevant data was missed, a survey of the gray literature was conducted using the databases of theses and dissertations from the following sources: the Coordination of Improvement of Higher Education Personnel (CAPES), the Digital Library of theses and dissertations of the Federal University of Viçosa, and the Brazilian digital library of theses and dissertations to ensure that no important studies were missed out. Next, the abstracts of these articles were analyzed to verify compliance with the inclusion criteria, and full-text articles were subsequently examined to confirm their eligibility.

SELECTION CRITERIA

In this review, we included randomized clinical studies that examined the efficacy of prebiotic, probiotic, or symbiotic supplementation in modulating intestinal microbiota and regulating nitrogen products and inflammation in CKD patients (both sexes) who had received the intervention for at least one day. Review articles, animal studies, articles not written in English, and those not related to the topic of interest were excluded.

DATA EXTRACTION AND SYNTHESIS

All relevant studies identified in the electronic databases were consolidated in a single database to remove all duplicates. After exclusion of the duplicates, two independent reviewers selected the references in three phases: analyses of titles, abstracts, and full texts. Any disagreements related to conflicting data or study eligibility were resolved by a third reviewer. Data including methodological quality, participant information, duration of intervention, and outcome type (changes in intestinal microbiota, nitrogen products, uremic toxins, total

cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, and inflammatory markers) were extracted and collected in duplicates in a Microsoft Excel worksheet. The quality of the included trials was measured using the Cochrane Collaboration's tool for assessing the risk of bias in randomized trials (23). Quality assessment was conducted by three independent reviewers, and disagreements were resolved by consensus.

RESULTS

SEARCH RESULTS

During the initial selection process, 1,679 articles were identified. Later, 781 duplicate articles were excluded, and 890 articles were removed after reading their titles and/or abstracts. Eight other articles were identified by reverse search and were considered as eligible; however, after reading their abstracts, six did not meet the inclusion criteria and were thus excluded from this study. Finally, we included and critically analyzed a total of ten articles (Fig. 1).

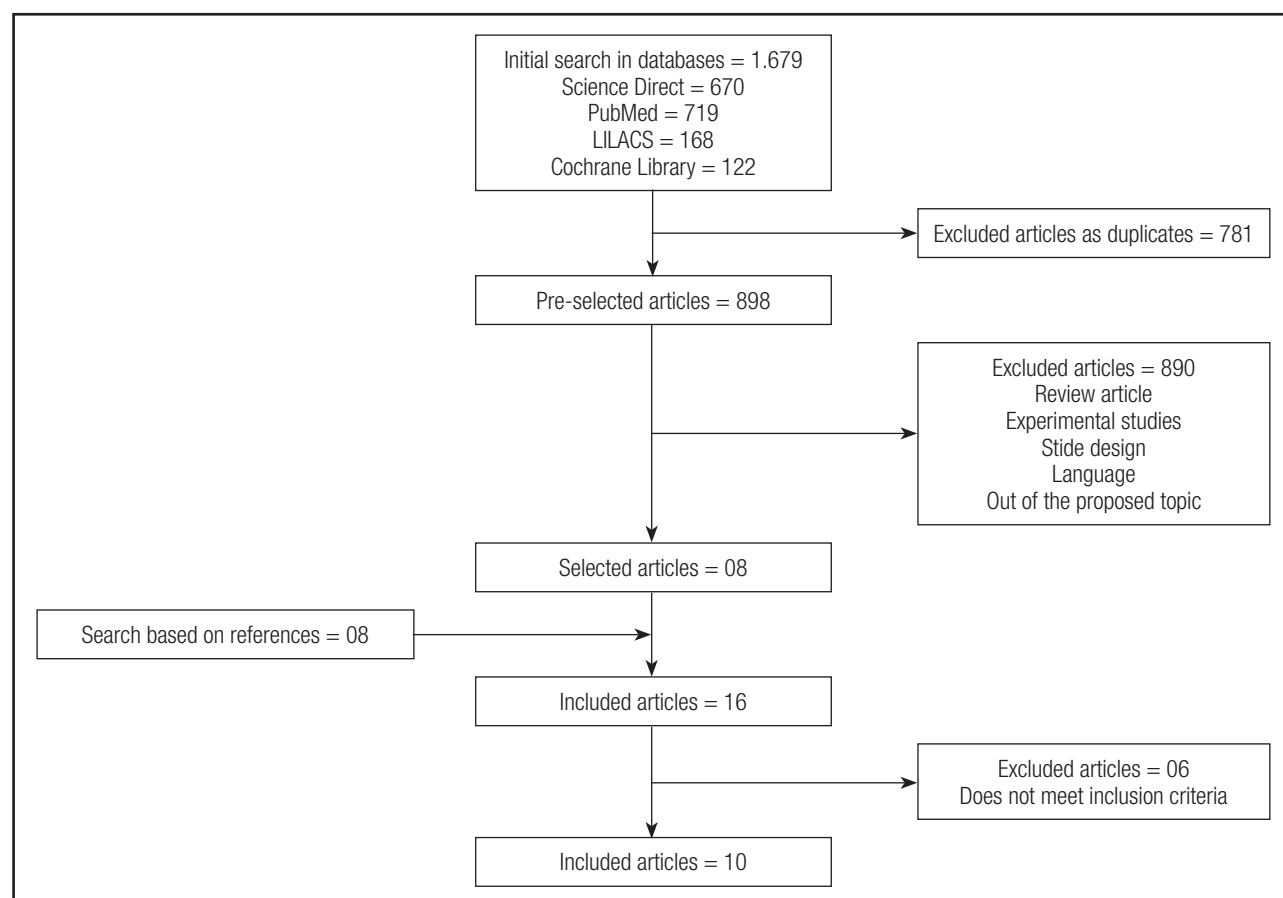


Figure 1.

Flowchart of the steps for obtaining the articles selected for this systematic review.

According to the Cochrane Collaboration's risk of bias tool for randomized trials, ten selected studies presented varying degrees of bias. All trials had a low or an unclear risk of bias for sequence generation, allocation concealment, blinding, selective outcome reporting, and other sources of bias.

STUDY CHARACTERISTICS

The selected articles described studies involving CKD outpatients who were either in stages 3-4 of the disease (five studies), stages 4-5 without dialysis (one study), or were receiving HD (four studies). These studies were further grouped based on the type of supplement that was used for treating the participating patients (Table I). While two studies tested the effectiveness of prebiotic products in patients with CKD, the remaining eight studies investigated the efficacy of either probiotics (four studies) or symbiotics (four studies) in these patients.

PARTICIPANT CHARACTERISTICS

A total of 423 subjects participated in the clinical trials, and the sample size ranged from 12 to 125. Their mean age ranged from 26 to 82 years and 64.18% of the participants were male. The sample sizes of three studies were similar, all of which involved patients with stages 3-4 of the disease (Table I).

INTERVENTIONS

Interventions with prebiotics in HD patients showed that the consumption of dietary fermentable fiber (10 g and 20 g for six weeks) and the consumption of lactulose (30 mm three times a day for eight weeks) improved lipid profiles (total cholesterol and LDL) and oxidative status (increased total antioxidant capacity and decreased malondialdehyde), suppressed the systemic inflammatory responses (TNF- α , IL-6, IL-8, and CRP), and increased bifidobacteria and lactobacillus counts (24,25).

Probiotic supplementation used in outpatient treatment (16×10^9 colony forming unit [CFU]/day of *Lactobacillus casei shirota* for two months; and 9×10^9 CFU/day of *Lactobacillus acidophilus* [*L. acidophilus*], *Bifidobacterium longum* [*B. longum*], and *Streptococcus thermophilus* [*S. thermophilus*] for three months) decreased the concentrations of blood urea and uremic toxins in treated patients. In addition, HD patients who received 2×10^9 CFU/day of *B. longum* demonstrated a reduction in their serum phosphate concentrations (26-28). However, probiotics had no effect on uremic toxin levels or inflammatory markers in HD patients who used 1.8×10^{11} CFU/day of *S. thermophilus*, *L. acidophilus*, and *B. longum* for two months (29).

Effects of symbiotics were studied in patients receiving outpatient treatment and those receiving HD. An increase in the *Bifidobacterium* population was observed in subjects who consumed

a symbiotic containing *L. acidophilus*, *Bifidobacterium bifidum* (2×10^{12} CFU/day), and inulin (2.31 g) for two months. A reduction in serum p-cresol concentration and an increase in stool volume were observed in patients who received 5×10^9 CFU/day Probinul neutro® for four weeks. An intake of symbiotic supplement with seven strains of probiotics and fructooligosaccharides (500 mg twice a day for six weeks) reduced blood urea nitrogen in patients with CKD stages 3 and 4. The symbiotic intervention that used three different types of fibers (15 g) and a combination of probiotics (*Lactobacillus*, *Bifidobacterium*, and *Streptococcus* genus [9×10^{10} CFU] for six weeks [4-week washout]) also showed an increase in the *Bifidobacterium* population and a reduction in serum p-cresol concentration (30-33).

DISCUSSION

In CKD, oxidative stress and inflammation occurs at the onset of the disease and increases with its progression. HD individuals experience increased oxidative stress possibly due to loss of antioxidants during dialysis, interactions between blood and dialysis membrane, and malnutrition (34). However, despite the fact that HD patients present greater oxidative stress and inflammation than other outpatient-treated patients, the results of selected studies indicate that the consumption of prebiotic (24,25), probiotic (26-29), and symbiotic (30-33) supplementation causes positive changes in HD and CKD patients.

Prebiotics are non-digestible food compounds that stimulate the beneficial growth of microbiota conferring health benefits to the host. They decrease oxidative stress, systemic inflammation, and the production of uremic solutes in CKD patients (35,36). In a randomized placebo-controlled trial, prebiotic consumption for six weeks by individuals receiving HD was associated with the following changes: reduced levels of total cholesterol and LDL, increased oxidative stress through reduction of malondialdehyde and increase of total antioxidant capacity, and improvement in systemic inflammation (TNF- α , IL-6, IL-8 and CRP) (24). These effects may be due to the ability of dietary fibers to hinder the process of dietary fat digestion and absorption, and favor the production of short chain fatty acids. During micelle formation phase of the digestion process, dietary fibers bind to cholesterol or bile acids forming a gel. This binding reaction delays gastric emptying, decreases dietary fat absorption and bile acid reabsorption by the enterohepatic circulation, and drives the use of hepatic cholesterol for bile acid production (37). Dietary fibers are not digested by humans; they are rather fermented by the intestinal bacteria that release short chain fatty acids. These fatty acids are responsible for modulating the intestinal microbiota and exerting immunomodulatory effects (31,37). Such changes in the intestinal microbiota were observed in a randomized controlled clinical trial. In this study, 30 mm of lactulose supplement three times a day for eight weeks increased bifidobacteria and lactobacillus counts in HD patients (25).

Probiotics are live microorganisms that, when administered in appropriate amounts, may confer benefits to the host's health (27).

Table I. Characteristics of selected studies and their major results

Author Year	Study design	Patients n	Intervention	Duration	Major results	Conclusion
Xie et al. (2015) (24)	Randomized, placebo control	HD G1 n = 42 G2 n = 39 GC n = 44	Prebiotic - Soluble fiber with more than 75% of fermentability G1 - 10 g G2 - 20 g GC - without fibers	6 weeks	↓ TC, LDL and TC/LDL relationship; ↓ MDA; ↓ TNF- α , IL-6, IL-8 e CRP; ↑ TAC	In patients on hemodialysis, fermentable fiber in the diet supplementation: – Improves the lipid profile and oxidative stress – Decreases the systemic inflammatory state
Tayebi-Khosroshahi et al. (2016) (25)	Randomized, placebo control	Outpatient on stage 3 and 4* GC n = 16 GT n = 16	Lactulose 30 mm syrup three times a day	8 weeks	↑ Bifidobacteria and Lactobacillus	The prebiotic will increase Bifidobacteria and Lactobacillus counts in patients with CKD
Ranganathan et al. (2009) (27)	Randomized, placebo control, double-blind, crossover	Outpatient on stage 3 and 4* GC = 13 GT = 13	Probiotics L. acidophilus B. longum S. thermophilus 9 x 10 ¹⁰ CFU/day	3 months	↓ Urea nitrogen and uric acid	The probiotic intake was well tolerated, with a reduction in the concentrations of urea nitrogen and uric acid, being able to contribute to a better quality of life
Ogawa et al. (2012) (28)	Placebo control	HD GC = 15 GT = 15	Probiotics: B. longum in tablets JBL01/day 2 x 10 ⁹ CFU/day	4 weeks	↓ Phosphate	B. longum can be used to treat hyperphosphatemia in patients on hemodialysis
Alatrste et al. (2014) (26)	Randomized	Outpatient on stages 3 and 4 n = 15	Probiotic: L. casei shirota G1 - 8 x 10 ⁹ CFU/day G2 - 16 x 10 ⁹ CFU/day	2 months	G2: larger reduction urea	Dose of 16 x 10 ⁹ CFU resulted in a greater reduction in blood urea levels
Natarajan et al. (2014) (29)	Randomized, placebo control, double-blind, crossover	HD GC = 22 GT = 22	Probiotics: S. thermophilus L. acidophilus B. longum 1.8 x 10 ¹¹ CFU/day	2 months	Trend to reduce CRP, total indoxil glucuronil and white blood cells	The use of probiotics seems to be safe and well tolerated
Cruz-Mora et al. (2014) (30)	Randomized, placebo control, double-blind	HD GT n = 8 GC n = 10	Synbiotic: L. acidophilus B. bifidum (2 x 10 ¹² CFU/day) Inulin (2.31 g)	2 months	↑ Bifidobacterium	Synbiotics can increase the bifidobacterium population maintaining the balance of intestinal microflora

(Continue in the next page)

Table I (Cont.). Characteristics of selected studies and their major results

Author Year	Study design	Patients n	Intervention	Duration	Major results	Conclusion
Guida et al. (2014) (31)	Randomized, placebo control double-blind	Outpatient on stages 3 and 4 GT n = 18 GC n = 12	Synbiotic 5 x 10 ⁹ CFU/day Probiol neutro®	4 Week	↓ p-cresol	Synbiotic lowers serum concentration of p-cresol in patients with CKD not subject to dialysis
Delghani et al 2016 (32)	Randomized, placebo control double-blind	Outpatient on stages 3 and 4 GT n = 18 GC n = 12	Synbiotics: L. casei, L. acidophilus L. bulgaricus L. rhamnosus B. breve B. longum, S. thermophilus Fructo-oligosaccharides (1,000 mg/day)	6 weeks	↓ Blood urea nitrogen	The intake of synbiotic supplement could reduce blood urea nitrogen in patients with CKD in stages 3 and 4
Rossi et al. 2016 (33)	Randomized, placebo control double-blind crossover	Outpatient on stages 4 and 5 n = 31	Synbiotics: Lactobacillus, Bifidobacteria, Streptococcus (9 x 10 ¹⁰) inulin fructo-oligosaccharides, galacto-oligosaccharides (15 g)	6 weeks (4-week washout)	↓ p-cresol ↓ Ruminococcaceae ↑ Bifidobacteria	In patients with CKD, synbiotics did decrease serum p-cresol and favorably modified the stool microbiome

GT1: group 1; GT2: group 2; GT3: group 3; GC: group control; GT: group test; IS: indoxyl sulfate; NF-κB: nuclear factor kappa beta; TC: triglycerides; CRP: C-reactive protein; TAC: total antioxidant capacity; MDA: malondialdehyde; TNF-α: tumor necrosis factor α; IL 6: interleukin 6; IL 8: interleukin 8; *Phases 3 and 4: phase of the chronic kidney disease preceding the hemodialysis phase.

Their effect on the immune system is evidenced by an increased expression of anti-inflammatory cytokines (interleukin 10 and nuclear factor kappa b), and a decrease in proinflammatory cytokines (interleukin 6 and TNF α) and levels of systemic inflammation (38,39).

In a randomized clinical trial, the consumption of probiotics containing 16×10^9 CFU/day of *L. casei shirota* for two months reduced the levels of serum urea in uremic patients with moderate to severe CKD (stages 3-4) (26). Similar results were observed in a pilot study that tested the effects of a probiotic containing different bacterial strains (*L. acidophilus*, *B. longum*, and *S. thermophilus*) at a dose of 9×10^9 CFU/day. After three months, the majority of the participants who received probiotic had reduced concentrations of serum urea nitrogen and uric acid, contributing to a better quality of life for those individuals (27). Oral administration of *B. longum* capsules in a placebo-controlled clinical trial was shown to reduce serum phosphorus concentrations in HD patients (28). This suggests that the reduction of these metabolites in CKD patients may be associated with the ability of the microbiota to use the metabolic waste as a substrate. A possible explanation for the observed reduction in uremia is related to the ability of certain anaerobic bacteria to degrade urea and uric acid through the production of enzymes, such as uricase, allantoinase, and urease. In an *in vitro* study, *Lactobacillus* exposure to an urea-enriched environment induced the production of enzymes responsible for urea reduction (40). Following the intake of probiotics, an increase

in *Lactobacillus* and *Streptococcus* populations in the feces can be explained by the conversion of urea to ammonia, a source of nitrogen for metabolic purposes (27). Probiotics can increase dietary fiber fermentation, reduce the intestinal pH, modulate the intestinal microbiota, and increase calcium ionization. Calcium, in turn, binds to phosphorus, reducing its absorption and leading to a reduction in serum phosphorus concentration (28). On the other hand, serum levels of uremic toxins and inflammatory markers were not affected in HD individuals who received a daily dose of 1.8×10^{11} CFU/day of a probiotic (containing *S. thermophilus*, *L. acidophilus*, and *B. longum*) for two months. However, the results showed a trend for the reduction of C-reactive protein ($p = 0.071$), indoxyl glucuronide ($p = 0.058$), and white blood cell counts ($p = 0.057$) (29). We believe that if the probiotics were administered in combination with soluble fibers, the results would have been different; this is based on our knowledge that soluble fibers can potentiate the effects of probiotics, resulting in a reduction of these markers. A decrease in uremic toxin concentration may be associated with fermentation of soluble fiber by intestinal anaerobic bacteria. This process of fermentation increases the production of short chain fatty acids and reduces colonic pH. The modified environment favors the growth of beneficial bacteria, inhibits the enzymes involved in generation of p-cresyl sulfate and indoxyl sulfate, improves epithelial barrier function (via induction of mucin production, blocking epithelial binding receptors, and strengthening

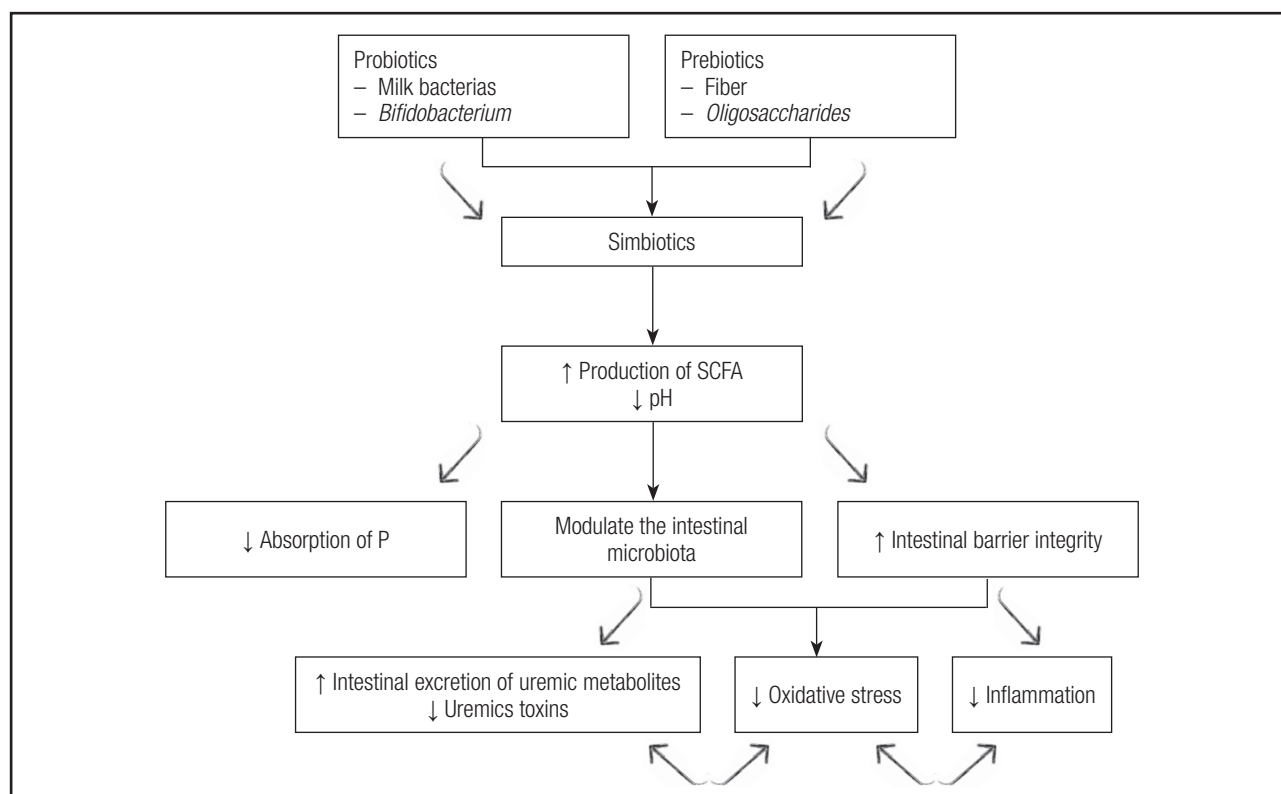


Figure 2.

Potential mechanisms involved in the modulation of intestinal microbiota and the reduction of oxidative stress and inflammation by pre- and/or probiotic products in chronic kidney disease. SCFA: short-chain fatty acids; P: phosphorus.

epithelial tight junctions), and reduces the influx of uremic toxins (41) (Fig. 2).

Supplementation of a symbiotic compound containing *L. acidophilus* and *B. bifidum* (2×10^{12} CFU/day) and inulin (2.31 g) for two months improved intestinal dysbiosis in individuals receiving HD, increasing the population of *Bifidobacterium* and preserving the numbers of *Lactobacillus* in the gut (30). Symbiotic intake in different stages of CKD decreased p-cresol serum concentration and normalized bowel habits (31,33). The symbiotic supplement (seven strains of probiotics and fructooligosaccharides), when consumed 500 mg twice a day for six weeks, can reduce blood urea nitrogen in patients with CKD at stages 3 and 4. One of the mechanisms by which this supplementation can potentially benefit the kidneys is by stimulating growth of gut microbial biomass by increased consumption of dietary fibers; this subsequently decreases ammonia production, increases the ratio of ionized ammonia, and facilitates the use of nitrogenous wastes by bacterial cells. Thus, more ammonia is excreted through the feces, and there is a low level production of potentially damaging forms of nitrogen, such as urea, uric acid, and creatinin (32). These results indicate the need to conduct a study to assess microbiota composition, uremic parameters, and inflammatory biomarkers in response to consumption of symbiotics.

In summary, the mechanism by which prebiotics and/or probiotics modulate the intestinal microbiota and decrease oxidative stress and inflammation may be due to increased intestinal anaerobic bacteria count and maintenance of intestinal barrier integrity (Fig. 2). Intestinal barrier integrity may be improved by the production of mucin, blocking of connection receptors, and strengthening of the epithelial junctions (17).

Due to the inclusion and exclusion criteria adopted in this study, we could include only ten studies in our review, and this limitation did not allow us to carry out a meta-analysis study. Our search for relevant studies was confined to the main databases; thus, it is possible that we might have limited our numbers by missing out some studies that fulfilled our inclusion criteria. Nonetheless, despite these limitations, the present study allowed us to identify "the gaps" in the literature in relation to the topic of interest, allowing us to propose future studies to unravel the mechanisms by which the prebiotics and/or probiotics can control progression of CKD.

CONCLUSIONS

Prebiotics and/or probiotics can modulate the intestinal microbiota by promoting the growth and metabolism of anaerobic bacteria, decreasing the production of uremic solutes, and resulting in oxidative stress and systemic inflammation. There is scarcity of studies that address the effects of prebiotics and/or probiotics on the intestinal microbiota, oxidative stress, and inflammation in CKD patients. Therefore, future studies are needed to provide clarification on topics, such as mechanisms that link regulation of dysbiosis and manifestation of diseases associated with CKD or

its precursor diseases, such as diabetes mellitus, hypertension, and atherosclerosis.

REFERENCES

1. Fasset RG, Venuthurupalli SK, Gobe GC, Coombes JS, Cooper MA, Hoy WE. Biomarkers in chronic kidney disease: a review. *Kidney Int* 2011;80:806-21.
2. Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, et al. Prevalence of chronic kidney disease in the United States. *J Am Med Assoc* 2007;298:2038-47.
3. Ramírez Bravo AM, Ramos Chevaile A, Hurtado Torres GF. Composición corporal en pacientes con insuficiencia renal crónica y hemodiálisis. *Nutr Hosp* 2010;25:245-9.
4. Sesso RC, Lopes AA, Thomé FS, Lugon JR, Martins CT. Brazilian Chronic Dialysis Survey 2016. *J Bras Nefrol* 2017;39:261-6.
5. SBN. Sociedade Brasileira de Nefrologia. Censo 2013. Available from: http://www.sbn.org.br/pdf/censo_2013-14-05.pdf
6. Ikizler TA, Pupim LB, Brouillette JR, Levenhagen DK, Farmer K, Hakim RM, et al. Hemodialysis stimulates muscle and whole body protein loss and alters substrate oxidation. *Am J Physiol Endocrinol Metab* 2002;282:E107-16.
7. Vaziri ND, Yuan J, Rahimi A, Ni Z, Said H, Subramanian VS. Disintegration of colonic epithelial tight junction in uremia: a likely cause of CKD-associated inflammation. *Nephrol Dial Transplant* 2012;27:2686-93.
8. Vaziri ND, Wong J, Pahl M, Piceno YM, Yuan J, Desantis TZ, et al. Chronic kidney disease alters intestinal microbial flora. *Kidney Int* 2013;83:308-15.
9. Kang JY. The gastrointestinal tract in uremia. *Dig Dis Sci* 1993;38:257-68.
10. Vaziri ND, Freel RW, Hatch M. Effect of chronic experimental renal insufficiency on urate metabolism. *J Am Soc Nephrol* 1995;6:1313-7.
11. Vaziri ND, Wong J, Pahl M, Piceno YM, Yuan J, DeSantis TZ, et al. Chronic kidney disease alters intestinal microbial flora. *Kidney Int* 2013;83:308-15.
12. Ramezani A, Raj DS. The gut microbiome, kidney disease, and targeted interventions. *J Am Soc Nephrol* 2014;25:657-70.
13. Poesen R, Meijers B, Evenepoel P. The colon: an overlooked site for therapeutics in dialysis patients. *Semin Dial* 2013;26:323-32.
14. Anders H, Andersen K, Stecher B. The intestinal microbiota, a leaky gut, and abnormal immunity in kidney disease. *Kidney Int* 2013;83:1010-6.
15. Shema-Didi L, Sela S, Ore L, Shapira G, Geron R, Moshe G, et al. One year of pomegranate juice intake decreases oxidative stress, inflammation, and incidence of infections in hemodialysis patients: a randomized placebo-controlled trial. *Free Radic Biol Med* 2012;53:297-304.
16. Celik G, Capraz I, Yontem M, Bilge M, Unaldi M, Mehmetoglu I. The relationship between the antioxidant system, oxidative stress and dialysis-related amyloidosis in hemodialysis patients. *Saudi J Kidney Dis Transplant* 2013;24:1157-64.
17. Rossi M, Johnson DW, Morrison M, Pascoe E, Coombes JS, Forbes JM, et al. Symbiotics easing renal failure by improving gut microbiology (SYNERGY): a protocol of placebo-controlled randomised cross-over trial. *BMC Nephrol* 2014;15:106-15.
18. Rossi M, Campbell KL, Johnson DW, Stanton T, Haluska BA, Hawley CM, et al. Uremic toxin development in living kidney donors: a longitudinal study. *Transplantation* 2014;97:548-54.
19. Nagalingam NA, Lynch SV. Role of the microbiota in inflammatory bowel diseases. *Inflamm Bowel Dis* 2012;18:968-84.
20. Vaziri ND, Zhao YY, Pahl M V. Altered intestinal microbial flora and impaired epithelial barrier structure and function in CKD: the nature, mechanisms, consequences and potential treatment. *Nephrol Dial Transplant* 2016;31:737-46.
21. Rossi M, Campbell KL, Johnson DW, Stanton T, Vesey DA, Coombes JS, et al. Protein-bound uremic toxins, inflammation and oxidative stress: a cross-sectional study in stage 3-4 chronic kidney disease. *Arch Med Res* 2014;45:309-17.
22. Moher D, Liberati A, Tetzlaff J, Altman DG. Academia and clinic annals of Internal Medicine preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. *Annu Intern Med* 2009;151:264-9.
23. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
24. Xie L-M, Ge Y-Y, Huang X, Zhang Y-Q, Li J-X. Effects of fermentable dietary fiber supplementation on oxidative and inflammatory status in hemodialysis patients. *Int J Clin Exp Med* 2015;8:1363-9.
25. Tayebi-Khosroshahi H, Habibzadeh A, Niknafs B, Ghotaslou R, Yeganeh SF, Ghojzadeh M, et al. The effect of lactulose supplementation on fecal micro-

- flora of patients with chronic kidney disease; a randomized clinical trial. *J Ren Inj Prev* 2016;5:162-7.
26. Alatrste PVM, Arronte RU, Espinosa COG, Cuevas MLAE. Effect of probiotics on human blood urea levels in patients with chronic renal failure. *Nutr Hosp* 2014;29:582-90.
 27. 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.
 28. 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.
 29. Natarajan R, Pechenyak B, Vyas U, Ranganathan P, Weinberg A, Liang P, et al. Randomized controlled trial of strain-specific probiotic formulation (Renadyl) in dialysis patients. *Biomed Res Int* 2014;2014:1-9.
 30. Cruz-Mora J, Martínez-Hernández NE, Campo-López MCF, 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.
 31. Guida B, Germanò R, Trio R, Russo D, Memoli B, Grumetto L, et al. Effect of short-term symbiotic treatment on plasma p-cresol levels in patients with chronic renal failure: a randomized clinical trial. *Nutr Metab Cardiovasc Dis* 2014;24:1043-9.
 32. Dehghani H, Heidari F, Mozaffari-Khosravi H, Nouri-Majelan N, Dehghani A. Symbiotic supplementations for azotemia in patients with chronic kidney disease: a randomized controlled trial. *Iran J Kidney Dis* 2016;10:351-7.
 33. Rossi M, Johnson DW, Morrison M, Pascoe EM, Coombes JS, Forbes JM, et al. Symbiotics easing renal failure by improving gut microbiology (SYNERGY): a randomized trial. *Clin J Am Soc Nephrol* 2016;11:223-31.
 34. Coombes JS, Fasset RG. Antioxidant therapy in hemodialysis patients: a systematic review. *Kidney Int* 2012;81:233-46.
 35. Furuse SU, Ohse T, Jo-Watanabe A, Shigehisa A, Kawakami K, Matsuki TC, et al. Galacto-oligosaccharides attenuate renal injury with microbiota modification. *Physiol Rep* 2014;2:1-13.
 36. Borges NA, Farage NE, Barros AF, Ferreira DC, Fouque D, Mafra D. Symbiotic supplementation promotes improvement of chronic diarrhea of unknown etiology in patient with chronic kidney disease and provides better outcomes in dialysis. *Nutr Hosp* 2016;33:182-4.
 37. Narayan S, Lakshmi Priya N, Vaidya R, Bai MR, Sudha V, Krishnaswamy K, et al. Association of dietary fiber intake with serum total cholesterol and low density lipoprotein cholesterol levels in urban Asian-Indian adults with type 2 diabetes. *Indian J Endocrinol Metab* 2014;18:624-30.
 38. Saulnier DM, Spinler JK, Gibson GR, Versalovic J. Mechanisms of probiosis and prebiosis: considerations for enhanced functional foods. *Curr Opin Biotechnol* 2009;20:135-41.
 39. Kirk J, Dunker KS. Dietary counseling: the ingredient for successfully addressing the use of herbal supplements and probiotics in chronic kidney disease. *Adv Chronic Kidney Dis* 2014;21:377-84.
 40. Chow KM, Liu ZC, Prakash S, Chang TMS. Free and microencapsulated *Lactobacillus* and effects of metabolic induction on urea removal. *Artif Cells Blood Substit Immobil Biotechnol* 2003;31:425-34.
 41. Rossi M, Kerenaftali K, Johnson DW, Campbell KL. Pre-, pro-, and symbiotics: do they have a role in reducing uremic toxins? A systematic review and meta-analysis. *Int J Nephrol* 2012;2012:1-20.