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The Role of Dietary Fiber and Prebiotics in Chronic Kidney Disease Gut Microbiota

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Abstract

Gut microbiota is defined as the community of microorganisms that colonizes the gastrointestinal tract and it develops a major role in maintaining host homeostasis by regulating several metabolic and immunological pathways. The imbalance of the gut microbiome, known as dysbiosis, has been described in numerous diseases including chronic kidney disease. Emerging evidence has shown that gut microbiota-targeted nutritional interventions, specially those based in high-fiber intake and prebiotic supplementation, can decrease CKD progression and ameliorate its comorbidities. A fiber intake of 25 - 30/day and prebiotic foods have displayed several beneficial effects including a decreased production and retention of gut-uremic toxins, a reduction of systemic inflammation and oxidative stress, an improvement in gut barrier integrity, as well as enhance the growth of saccharolytic bacterial species and a deceleration in kidney disease progression, attenuating its comorbidities. However, recommendations on whole dietary patterns would be more adequate than limiting advice to adopting a nutrient-focused perspective. Further long-term clinical trials will be needed in order to assess fiber and prebiotic supplementation effects in these patients.

Keywords: chronic kidney disease; diet; dietary fiber; dysbiosis; gut microbiota; prebiotics

1. Introduction

Gut microbiota (GM) is defined as the community of microorganisms that colonizes the gastrointestinal tract. It is composed by a large amount of bacterias as well as other microorganisms such as archaea, fungi and viruses [1]. These bacterias are clustered in five predominant phyla: *Firmicutes* (*Lactobacillus, Ruminococcus, Faecalibacterium, Roseburia*) and *Bacteroidetes* (*Bacteroides, Prevotella*) which constitute 90%, followed by *Actinobacteria (Bifidobacteria), Verrucomicrobia* (*Akkermansia muciniphila*) and *Proteobacteria* (*Escherichia coli, Salmonella*) [2]. Bacterial density progressively increases along the gastrointestinal tract reaching up to 10^{12} CFU/g in the colon [1].

Microbiota develops a major role in maintaining host homeostasis by regulating several metabolic and immunological pathways [1]. It is involved in dietary fiber fermentation and short-chain fatty acids (SCFAs) production. Furthermore, it participates in the synthesis of vitamin K and B, amino acids and neurotransmitters (dopamine, serotonin) release [1,2], as well as calcium and iron absorption. Moreover, microbiota takes part in immune system maturation and activation, it regulates host immune response, and it helps to maintain gut epithelial barrier integrity protecting against pathogens [1].

The imbalance of the gut microbiome, known as dysbiosis, has been described in numerous diseases including chronic kidney disease (CKD) [2-5]. In these patients, dysbiotic microbiome is characterized by changes in bacterial proportion, diversity and richness (lower symbiotic bacteria) and the overgrowth of certain bacterial species which can have a detrimental effect on the host [2]. This condition is produced as a consequence of kidney disease progression, gut-derived uremic toxins (indoxyl sulfate, trimethylamine-N-oxide, p-cresyl sulfate) and ammonia retention, pharmacological treatment (phosphate binders, antibiotics, iron supplements), polypharmacy and dietary restriction of potassium-rich and phosphorus-rich foods, that sometimes lead to lower fiber intake [4].

In patients suffering from chronic kidney disease, nutritional management is crucial to decelerate disease progression [3]. Emerging evidence has shown that gut microbiota-targeted nutritional interventions can decrease CKD progression and ameliorate its comorbidities [4,5]. In this context, dietary fiber and prebiotics have demonstrated to beneficially modulate microbiota composition and activity, which may be an interesting therapeutic target in patients with CKD to improve clinical outcomes [3,5,6].

This review summarizes the role of dietary fiber and prebiotics in the gut microbiome modulation in patients with chronic kidney disease (CKD), as well as disease progression and its associated comorbidities.

2. Dietary Fiber

According to the European Food Safety Authority (EFSA), dietary fiber is defined as carbohydrates plus lignin which are not digested in the intestinal tract [7-9]. Plant-based foods are the main dietary fiber sources (grains, legumes, nuts, seeds, fruits, vegetables) [8,10], but it can also be added to some products [8]. Fiber is currently classified according to its physicochemical characteristics of viscosity, water-solubility and fermentability, among others [9,11], which determine its physiological effects. In line with water-solubility capacity, soluble fibers (inulin, pectins, oligosaccharides, β-glucans, gums) are known to be the most fermentable ones by the gut microbiota, whereas insoluble fibers (hemicellulose, cellulose, wheat bran, lignin) are barely or non-fermentable by GM [10,11].

Nutrition nephrology guidelines KDOQI and KDIGO do not provide any specific dietary fiber intake guidance for CKD patients, thus the recommendation on fiber intake is the same as the general population (between 25 - 30g/day) [10].

Evidence suggests that dietary fiber intake has several benefits on chronic kidney disease patients, due to its effect on microbiota modulation [8,10,11]. Regarding its physiological effects, it improves glucose and lipid metabolism and weight control (due to viscous fibers that reduce appetite) [10], lowers systemic inflammation, oxidative stress, metabolic acidosis [8], and mortality [10].
Also, due to its bulking effect, fiber seems to be beneficial in reducing constipation [10], which is one of the major gastrointestinal complications in CKD patients, especially in the ones who receive haemodialysis treatment [10,12]. Moreover, fiber intake has a major role in the modulation of the gut microbiota composition and functionalities promoting saccharolytic fermentation over proteolytic fermentation [8,10,13]. Enhancing saccharolytic fermentation and saccharolytic bacteria promotes SCFAs production, decreases gut-derived uremic toxins production, helps to maintain gut barrier integrity and lowers down inflammatory markers [8,10].

There is not enough evidence to conclude that dietary fiber has a direct effect on slowing down CKD progression [8], but regarding its effect on uremic toxins, a recent systematic review and meta-analysis showed that adequate fiber intake significantly reduce both creatinine and urea serum levels [14]. Supporting these results, further meta-analysis of randomized controlled trials conducted in 2021 concludes that dietary fiber supplementation can decrease gut-derived uremic toxins in patients with CKD [15].

It is important to consider that there is a direct relationship between protein/fiber ratio and uremic toxins indoxyl sulfate (IS) and p-cresyl sulfate (PCS) levels in patients with CKD. Therefore, increasing dietary fiber and decreasing the intake of animal products towards plant-based foods may be beneficial for these patients [8].

3. Prebiotics

Prebiotics are non-digestible food substances that selectively modify gut microbiota composition and activity conferring health benefits to the host and promote the growth of beneficial bacteria species [11,16,17]. They can be naturally found in plant-based foods such as fruits (bananas), vegetables (onions, garlic, artichokes) and cereals, but they can also be found in human milk, honey [16,18] and in cooked and cooled legumes, grains (rice) or tubers (potatoes) [19]. Prebiotic includes: resistant starch (RS), non-starch polysaccharides, inulin, fructooligosaccharides (FOS), galactooligosaccharides (GOS), and arabinoxylan oligosaccharides (AXOS) [18].

Literature suggests that prebiotics have potential beneficial effects in CKD patients, partly due to higher SCFAs production: they attenuate systemic inflammation and oxidative stress, they contribute to intestinal epithelial barrier integrity, and they can also decrease uremic dysbiosis by modifying microbiota composition, stimulating the growth and activity of beneficial bacteria including *Bifidobacteria* and *Lactobacilli* [10,11,16,19,20].

The effect of prebiotics in uremic retention solutes is not elucidated, as there is a considerable degree of variability and heterogeneity among studies. A clinical trial where CKD patients were randomly supplemented with FOS did not provide significant changes in serum levels of microbiota-derived uremic toxins, intestinal permeability and inflammatory markers [21]. In another study, CKD patients supplemented with AXOS showed lower trimethylamine-N-oxide (TMAO) levels, but did not show the same reduction in IS or PCS levels [22]. In addition, The TarGut-CKD study showed that oligofructose enriched inulin (p-inulin) supplementation significantly changed microbiota composition increasing *Bifidobacterium* and *Anaerostipes* abundance. However, there was no difference in IS or PCS plasma levels [23]. Conversely, few clinical trials showed a significant decrease in PCS serum levels with oligofructose-enriched inulin supplementation [24,25], and a significant decrease in IS plasma levels with GOS supplementation [26]. Moreover, in a longitudinal controlled clinical trial, inulin supplementation combined with a low-protein diet significantly improved inflammatory and metabolic parameters in patients with CKD by modulating gut microbiota and increased *Bifidobacterium* concentration [27]. Furthermore, resistant starch supplementation has proven to decrease PCS, IS, inflammatory markers and reactive oxygen species [28], as well as to promote beneficial bacteria and lower phenylacetic acid and phenylacetylglutamine serum levels [17]. A recent systematic review and meta-analysis of randomized controlled trials conclude that microbiota-targeted therapies based on prebiotic supplementation significantly decrease PCS serum levels in patients with CKD, but not IS concentration [29].

4. Limitations

Promoting high fiber intake and prebiotic supplementation can be challenging in patients with chronic kidney disease.

Firstly, attempting to achieve high-fiber intake or adding prebiotic foods remains a concern in CKD patients due to the risk of hyperpotassemia and hyperphosphatemia [9,10]. 2020 KDOQI guidelines recommend to individualize and adjust potassium intake when needed, and to reduce high-bioavailability sources of potassium and phosphorus such as processed and ultra-processed foods [30]. Ways to reduce potassium and phosphorus content from diet include, but are not limited to: i) specific cooking techniques (such as boiling or blanching), ii) consuming frozen and canned vegetables, iii) limiting processed foods or food that contains phosphorus and potassium additives or, straightforwardly, iv) having a plant-based diet, which has shown to reduce dietary acid load and to produce a basic net balance, reducing metabolic acidosis and balancing potassium levels [31].

Secondly, increasing dietary fiber may lead to gastrointestinal intolerance, especially in patients whose basal fiber consumption is very low [10].

Thirdly, there is limited evidence and short term follow-up interventions. Therefore, further long-term trials are needed to elucidate the better therapeutic strategies involving fiber and prebiotic intake and supplementation in patients with CKD, along with type and quantity of each fiber or prebiotic, and gastrointestinal tolerance.

To sum up, ensuring an adequate fiber intake or adding prebiotic foods may not be enough to obtain better outcomes in CKD patients, or effectively modulate gut microbiota to slow down disease progression and lower gut-uremic toxins production. Thus, a recommendation of whole dietary patterns, such as Mediterranean diet, Plant-Dominant Low-Protein (PLADO) diet or Dietary Approaches to Stop Hypertension (DASH) diet, might prove more beneficial for this purpose than adding individual foods to diet or providing nutrient-focused advice.

In spite of these limitations, patients with CKD should be recommended to increase their fiber intake, to take prebiotic supplementation and to include fermented foods or the ones that naturally contain prebiotics. These recommendations would aid in reducing dysbiosis and uremic toxins production and retention, decelerating disease progression and ameliorate associated comorbidities.

5. Conclusions

Fiber intake has a major role in modulating gut microbiota in chronic kidney disease patients. Gut microbiota-targeted nutritional interventions in CKD patients, involving dietary fiber (25 - 30 g/day) and prebiotics, have displayed the following beneficial effects: i) a decreased production and retention of uremic toxins, ii) a reduction of systemic inflammation and oxidative stress, iii) an improvement in gut barrier integrity, ameliorating uremic dysbiosis and enhancing the growth of saccharolytic bacterial species and saccharolytic fermentation over proteolytic fermentation, iv) a deceleration in disease progression, attenuating its comorbidities.

With regards to providing nutritional advice for CKD patients, recommendations based on whole dietary patterns would be more adequate than limiting advice to adding individual foods to diet or adopting a nutrient-focused perspective.

Notwithstanding the above, further long-term clinical trials will be needed in order to assess fiber and prebiotic supplementation effects and to ensure safety in patients with CKD.

Conflicts of Interest

Authors declare no conflict of interest.

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