Benefits of Probiotics on Chronic Kidney Disease

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ABSTRACT

Chronic kidney disease can result in changes in intestinal microbiota (*dysbiosis*) and the structure and function of the intestinal mucosa, which contribute to the pathogenesis of CKD progression. In CKD, there is a buildup of metabolic remnants known as a uremic toxin or uremic retention solute (URS), especially indoxyl sulfate and p-cresyl sulfate. Probiotics administration in CKD aims to reduce the synthesis of URS. A literature review indicates that probiotics are useful in patients with CKD, especially in stages 3 and 4. Some small-scale studies showed the benefits of giving probiotics in CKD, namely, reducing levels of albuminuria, BUN, serum creatinine, and levels of p-cresyl sulfate (PCS), increasing IL -6, as well as safe and effective administration for CKD.

Keywords: Probiotic, Uremic Retention Solute, Chronic Kidney Disease

I. INTRODUCTION

Chronic kidney disease (CKD) is an abnormalities of kidney structure and/or function present for > 3 months with implication for health. CKD criteria in the form of one or more markers of kidney damage are albuminuria (urinary albumin excretion ≥ 30 mg/24 hours, albumin-creatinine ratio ≥ 30 mg/g or ≥ 30 mg/mmol), urinary sediment abnormalities, electrolyte abnormalities and other abnormalities related to tubular disease, abnormalities ≥ 30 mg/g or ≥ 30 mg/mmol), urinary sediment abnormalities, electrolyte abnormalities, and other abnormalities related to tubular disease, abnormalities obtained from a histopathological examination, structural abnormalities detected from imaging studies, history of kidney transplantation and/or decreased glomerular filtration rate (GFR) < 60ml/min /1.73 m² [1]

Classification of CKD based on stage is divided into five; namely, stage 1 is kidney damage with standard or high glomerular filtration rate (90 ml/min/1.73m²); stage 2 is kidney damage with GFR mildly decreased (60-89 ml/min/1.73m²); stage 3 is kidney damage with GFR moderately decreased (30-59 ml/min/1.73m²); stage 4 is kidney damage with GFR severely decreased (15-29 ml/min/1.73m²); stage 5 is kidney failure (GFR < 15 ml/min/1.73m²) [2].

The gastrointestinal tract is a complex ecosystem with 10-100 trillion microorganisms called gut microbiota that plays a role in the body's biochemical activities. It is known that changes in intestinal microbiota can affect some aspects of biology and changes in function and composition called dysbiosis. In general, dysbiosis is defined as the composition and functional changes of microbiota compared to those found in healthy people. Dysbiosis is influenced by a series of environmental factors and host-realated, which disrupt the microbial ecosystem. Dysbiosis plays a role in the pathogenesis of various diseases, such as chronic inflammation, diabetes mellitus, obesity, cardiovascular disease, and CKD progression to some extent [3] [4].

The kidneys function to excrete the remnants of both nitrogen and non-nitrogen metabolism. In stage 4 and especially stage 5 of CKD, there is a buildup of metabolic remnants known as a uremic toxin or uremic retention solute (URS). Indoxyl sulfate and p-cresyl sulfate are two URS produced by microbiota, of which levels increase in CKD. Increased levels of indoxyl sulfate and p-cresyl sulfate are also caused by impaired excretion by the kidneys. Increased levels of these substances have been proven to play a role in the CKD progression [5] [6].

Probiotics are living microorganisms (bacteria) found in foods or food supplements that are the same as commensal microorganisms found in the human digestive tract. The prototypes of probiotics are *Lactobacillus* and *Bifidobacterium* [7].

In some studies, probiotics are useful in inhibiting CKD progression [7].

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II. LITERATURE REVIEW

Dysbiosis and Chronic Kidney Disease

Chronic kidney disease can cause significant changes in intestinal microbiota (dysbiosis), the structure and function of the intestinal mucosa. These changes contribute to the pathogenesis of CKD progression. In CKD, urea secretion into the intestine increases where urea is converted to ammonia by urease. The ammonia is converted to ammonium hydroxide, which will increase the pH and aerobic bacteria growth. Aerobic bacteria will produce URS, which will affect the production of protein-bound uremic toxins that contribute to physiological changes, including blood vessel damage and progressive kidney damage [4] [8] [9]. Another factor that causes dysbiosis is constipation, which can increase bacterial growth. Constipation is caused by many things, such as low fluid intake and high fiber foods, lack of physical activity, and iron therapy [5] [10] [11].

Food that is not absorbed in the small intestine is fermented quickly by the colonies of bacteria in the colon. The two main types of fermentation by bacteria are saccharolytic and proteolytic. In CKD patients, a decrease in fiber consumption can decrease saccharolytic. Saccharolytic is a good type of carbohydrate fermentation because it forms beneficial metabolites, including short-chain butyric, propionic, and acetate fatty acids. This short-chain fatty acid has anti-inflammatory properties. Fermentation of proteins is called proteolytic, which will form URS, such as indoxyl sulfate and p-cresyl sulfate [10] [12] [13].

Indoxyl sulfate is excreted by the kidneys but accumulated in CKD patients due to impaired kidney function. Indoxyl sulfate and p-cresyl sulfate induce oxidative and inflammatory stress, cause endothelial dysfunction, and increase blood vessel muscle cell proliferation [13].

Probiotic Microorganism

The majority of probiotic microorganisms belong to Lactobacillus and Bifidobacterium genera. However, some bacteria and fungi also have probiotic effects (table 1) [14].

<table>
<thead>
<tr>
<th>Lactobacilli</th>
<th>Bifidobacteria</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>L.acidophilus-group</td>
<td>B. longum (BB536)</td>
<td>Enterococcus faecalis</td>
</tr>
<tr>
<td>L.acidophilus (LA-5)</td>
<td>B. longum (SP 07/3)</td>
<td>Enterococcus faecium-</td>
</tr>
<tr>
<td>L.crispatus (Lacidophilus</td>
<td>B. bifidum (MF 20/5)</td>
<td>Lactococcus lactis</td>
</tr>
<tr>
<td>“Gilliland”)</td>
<td>B. infantis</td>
<td>Streptococcus thermophilus</td>
</tr>
<tr>
<td>L.johnsonii (LA 1)</td>
<td>B. animalis (B. animalis</td>
<td>Propionibacteria</td>
</tr>
<tr>
<td>L.gasseri (PA 16/8)</td>
<td>ssp. lactis BB-12</td>
<td>E.coli ( coli “Nissle</td>
</tr>
<tr>
<td>L.casei-group</td>
<td>B. adolescentis</td>
<td>1917”)</td>
</tr>
<tr>
<td>L.(para)casei</td>
<td>B. breve</td>
<td>Sporolactobac. Inulinus</td>
</tr>
<tr>
<td>(L.casei)”Shirotu”</td>
<td></td>
<td>S. Baciullus cereus</td>
</tr>
<tr>
<td>L.casei“defensis”</td>
<td></td>
<td>“toyoi”</td>
</tr>
<tr>
<td>L.rhamnosus (LGG)</td>
<td></td>
<td>Saccharomyces bauldarii</td>
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<tr>
<td>L.reuteri</td>
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<td>L.plantarum (299 and 299v)</td>
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</table>

Lactobacilli is a gram-positive bacterium that produces lactate and is the dominant microbiota in the intestines of healthy individuals. Bifidobacteria are the central part of normal intestinal microflora throughout human life. The number of bifidobacteria in the adult’s large intestine is 10^{10}-10^{11} colony forming units (cfu)/gram, but this number decreases with age. Bifidobacteria are non-motile stems; most strains are anaerobic [14].

The Use of Probiotics in Chronic Kidney Disease

The administration of probiotics in CKD is an adjuvant treatment. The primary purpose of giving probiotics to CKD is to reduce URS synthesis derived from protein breakdown, which cannot be entirely reduced by low protein intake [7].

Some of the mechanisms underlying the potential beneficial effects of probiotics are reducing inflammation, increasing epithelial barrier function, production and secretion of mucin, inhibiting adhesion of pathogenic bacteria,
and regulating epithelial cells homeostasis through specific cellular signal transduction pathways, and increasing cell survival [15].

Several small-scale studies have been conducted to identify the benefits of giving probiotics for CKD: (1) Research by Yacoub R et al analyzed NHANES data comparing the administration of a single probiotic and a probiotic along with yogurt against the dynamics of albuminuria and GFR [4]. In both groups of the studied subjects, the administration of single probiotic versus control and probiotics with yogurt versus control, after adjusting according to age, sex, race, hypertension, diabetes mellitus, body mass index, HbA1C, socioeconomic status, duration of use of probiotics/yogurt and drugs (Angiotensin-Converting Enzyme Inhibitors, Angiotensin Receptor Blockers, Statins, and Insulin) can reduce albuminuria by 36% in the group given probiotics along with yogurt; (2) Alatriste P et al. analyzed 30 CKD subjects by comparing the administration of lactobacillus casei shirota (LeS) dose of 8x10⁹ CFU and 16x10⁹ CFU in subjects with stage 3 and 4 CKD; (3) Jia L et al conducted a meta-analysis of 8 studies with 261 CKD subjects in stage 3-5, given probiotic supplementation [17]. It was found that probiotics reduced levels of p-cresyl sulfate (PCS) and increased levels of IL-6 that could protect the intestinal epithelial barrier in CKD subjects; (4) Ranganathan et al. showed that in 16 weeks administration of probiotics in rats with CKD could increase survival and decrease blood urea nitrogen (BUN) [18]; (5) Ranganathan et al. demonstrated that the administration of probiotics in subjects with stage 3 and 4 CKD could reduce BUN levels, improve quality of life, serum creatinine, and uric acid levels [19] [20]. Two pilot studies with six months probiotic administration found that probiotics were effective and safe in stage 3 and 4 CKD; (6) Eidi et al. showed that in 42 hemodialysis patients for 4 weeks showed lower levels of uremic toxin in the group given probiotics (Lactobacillus rhamnosus) [21]. Total levels of Phenols and p-cresols were associated with intakes of sodium, energy, carbohydrates, fats, proteins, and fiber, accompanied by hours of hemodialysis per week in linear regression analysis; (7) Non-randomized studies in 22 hemodialysis patients for 4 weeks who consumed a mixture of linear β and oligofructosa by Meijers et al showed that serum concentrations of p-cresyl sulfate at week 4 were significantly reduced by 20% (P = 0.01), the rate of p-cresyl sulfate formation decreased (P = 0.007). In contrast, neither the rate of indoxyl sulfate formation (P = 0.9) nor serum concentration (P = 0.4) changed significantly [22]. (8) Placebo-controlled randomized study by Natarajan et al assessed the safety and efficacy of the combination of S [23], thermophilus KB 19, L. acidophilus KB 27, and B. longum KB 3 as measured through improved quality of life or reduction of uremic toxin levels in CKD patients. The secondary goal is to investigate the effects on several biomarkers of inflammation and oxidative stress. The study was conducted for 2 months, with physical examination, venous blood collection, and quality of life questionnaire completed at each visit. In the study, a decrease in the number of leukocytes, and a decrease in the levels of C-reactive protein, and total indoxyl glucuronide were observed. No statistically significant changes were observed in other uremic toxin levels or quality of life measures. In this study, the combination of probiotics was generally safe to be given to CKD patients undergoing hemodialysis. Stability in the assessment of quality of life is a relatively good result for the group of patients in CKD; (9) The systematic review by Fagundes et al which aimed to systematically examine the effects of supplementation with probiotics in the treatment of CKD involved studies written in English and Portuguese published in the period 2012-2016 describing randomized clinical trials [24]. Eight of the 82 eligible articles met the inclusion criteria. The sample size ranged from 18 to 101 people with CKD. The duration of the included studies varied from four to 24 weeks. Most of the articles included reported positive effects on renal function and decreased levels of urea, blood urea nitrogen, ammonia, plasma p-cresol, p-cresyl sulfate, and indoxyl sulfate; (10) The meta-analysis by Abdul Qader et al. aimed to assess the effectiveness of probiotic supplementation in patients with diabetic nephropathy [25]. A literature search found 320 citations, after a screening process 8 studies were included in the meta-analysis. Type 2 DM patients with chronic kidney disease demonstrated that probiotic supplementation decreased serum insulin and insulin resistance, but had no beneficial effects on renal function, body weight, and lipid profile, with positive effects on several biomarkers of oxidative stress. In addition, consumption of soy protein containing probiotics may have a significant effect on kidney function and lipid profile, and this conclusion requires more trials to prove the benefits of this combination. In addition, trials with longer follow-up durations and larger sample sizes are needed to produce more valid results regarding the safety and efficacy of probiotic supplementation in type 2 DM patients with diabetic nephropathy.

III. CONCLUSION

Probiotics are living microorganisms (bacteria) found in food or food supplements, which are the same as commensal microorganisms found in the human digestive tract. Chronic kidney disease can cause significant changes in intestinal microbiota (dysbiosis), and the structure and function of the intestinal mucosa. These changes contribute to the pathogenesis of CKD progression. In CKD, there is a buildup of metabolic remnants known as a uremic toxin or uremic retention solute (URS). Probiotic administration in CKD is an adjuvant treatment aimed at

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