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Gut dysbiosis and the role of probiotics in chronic kidney disease

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ABSTRACT

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Chronic inflammatory condition in chronic kidney disease (CKD) patients is associated with increased risk of cardiovascular morbidity and mortality. Gut dysbiosis is assumed as one of leading factors to the chronic inflammatory condition. The relationship between the kidney and the gastrointestinal, knowns as the gut-kidney axis, has a role in production and accumulation of uremic toxins derived from gut microbial fermentation of protein, and translocation of endotoxins and microbial from gut lumen into bloodstream due to alterations of intestinal epithelial barrier in CKD patients. Probiotics supplementation is one of the optional therapy to restore the gut dysbiosis in CKD patients. Recent studies found that probiotics supplementation in CKD patients decreased uremic toxins and pro-inflammatory cytokines production, and delayed CKD progression. The improvement of this chronic inflammatory condition is expected to decrease cardiovascular disease risk in CKD patients. This review aims to describe the importance of gut-kidney axis in CKD patients, particularly in gut dysbiosis, and the role of probiotics in progression of CKD.

ABSTRAK

Keywords:
gut dysbiosis;
chronic kidney disease;
probiotics;
gut-kidney axis;
chronic inflammation

Kondisi inflamasi kronik pada penderita penyakit ginjal kronik (PGK) berhubungan dengan peningkatan risiko morbiditas dan mortalitas kardiovaskular. Salah satu sumber penyebab timbulnya inflamasi kronik ini adalah perubahan bakteri usus. Adanya hubungan antara ginjal dan saluran cerna pada penderita PGK ini disebut aksis usus-ginjal, yang berperan dalam hal produksi dan akumulasi toksin uremik hasil fermentasi protein oleh mikroflora usus, serta translokasi endotoksin dan mikroba dari lumen usus ke aliran darah akibat gangguan barier epitel usus. Salah satu alternatif memperbaiki kondisi disbiosis usus adalah dengan pemberian probiotik. Beberapa studi yang ada saat ini, menunjukkan bahwa pemberian probiotik pada penderita PGK dapat menurunkan produksi toksin uremik dan sitokin inflamasi, serta memperlambat progresi PGK. Dengan perbaikan kondisi inflamasi ini diharapkan akan menurunkan risiko penyakit kardiovaskular pada penderita PGK. Tujuan dari tinjauan ini adalah untuk memaparkan pentingnya aksis usus-ginjal pada penderita PGK, khususnya pada kondisi disbiosis mikrobiota usus, dan peran probiotik dalam menghambat perkembangan PGK.

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INTRODUCTION

Chronic kidney disease (CKD) is a global health problem with the prevalence around 11-13% in adults, that majority are on stage 3.¹ All stages of CKD are related to an increased risk of cardiovascular morbidity, early mortality, and decreased quality of life.^{1,2} Cardiovascular disease (CVD) is the most common cause of mortality in CKD patients, and the risk of mortality is not only associated with the common risk factors such as hypertension, diabetes, and dyslipidemia. Moreover, it also associated with non-conventional risk factors, such as chronic inflammation.²⁻⁴

Chronic inflammation in CKD or end-stage kidney disease (ESKD), whether it is related to dialysis or non-dialysis factors, is caused by the increased production of pro-inflammatory cytokines and decreased renal clearance, the interaction between the blood and dialyzer, unsterilized dialysis fluid, infection (primarily bacterial), inadequate intravenous iron supplementation, and other comorbidities such as heart failure.³

Several studies reported a strong relationship between gut and kidney in CKD. Although the clinical infection has not been observed, the typical inflammatory condition in CKD could be induced by the gut translocation of molecules and pro-inflammatory cytokines or gut microbiota translocation from gut into the vascular. Thus, the innate immunity is triggered by the bacteria structures, such as the lipopolysaccharides from the gram-negative bacteria cell wall and creates inflammation.⁵ Meanwhile, recent studies showed that uremia can affect the structure and functions of the gut barrier, and influence the inflammation in CKD.^{3,5-8}

This review aims to show the importance of the gut-kidney axis in CKD patients, especially gut dysbiosis, and

the role of probiotics in inhibiting the progression of CKD.

MATERIAL AND METHODS

Literature searches were performed on PubMed and Google Scholar without any restrictions. Free words and Medical Subject Headings (MeSH) were used to construct the search terms related to gut dysbiosis, probiotics, and chronic kidney disease. Eligible articles for further review were identified by screening of titles and abstracts, followed by a full-text review. In the case of multiple publications, the most recent and complete reports were included. Authors finalized the literature search on January 31, 2021.

RESULTS

A total of 75 articles from PubMed and 103 articles from Google Scholar were obtained at the start of the search. Sixty-four articles were removed due to duplication. We screened abstracts and conclusions of each literature. Sixty-eight literatures were excluded, and leaving 46 articles in hand. A more in-depth review of the literature excluded another 10 and we ended up with 36 articles.

DISCUSSION

The gut microbiota

Gut microbiota is microorganisms that inhabit the gut and have a symbiotic relationship with the host.^{3,6} The human gastrointestinal tract consists of almost 100 trillion microorganisms which are varied in species. As the oxygen level is decreased, the density of bacterial cells in the gastrointestinal tract is progressively increased and it may reach 10^{11} to 10^{12} /mL in the colon.^{6,9} Some phylums which predominant in the human intestine are Firmicutes, Bacteroidetes, Actinobacteria,

Proteobacteria, Fusobacteria, and Verrucomicrobia. Bacteroidetes (*Bacteroides*, *Provetella*, and *Xylanibacter*) and Firmicutes (*Ruminococcus*, *Clostridium*, *Lactobacillus*, *Eubacterium*, *Faecalibacterium*, and *Reseburia*) are the two most abundant phyla that makeup 90% of the microbiomes.^{3,9}

The gut microbiota confers roles in host health, such as protecting the gastrointestinal tract by adding additional metabolism pathways for certain substances (e.g. vitamins), energy production, and improving the immune system. It also contributes to the biotransformation of conjugated bile acids.^{3,10} Some physiological effects of gut microbiota are presented in TABLE 1.

The distal gut is a supportive environment for bacterial growth due to its high molecule concentration of nutrition for microbiota growth.³ The abundance of microbiota in each individual is particularly determined by the type of food consumed.^{6,9} Some carbohydrates and proteins which are not digested by some proximal gut are anaerobically metabolized by bacteria which is known as fermentation. Various fermentation products give different effects for each individual. Carbohydrate is an important nutrition in colonic microbe metabolism to produce energy and other end products such as methanes, hydrogens, and short-chain fatty acid (SCFA).^{3,6}

When the requirement of indigestible carbohydrate is not met, protein is used for bacterial growth and this condition negatively impact the growth of saccharolytic bacteria. In turn, the protein will be fermented by the proteolytic bacteria, such as *Clostridium* and *Bacteroides*, to produce energy by the deamination reaction. Nevertheless, this pathway produces potentially toxic metabolites (such as ammonia, amines, phenols, and indoles), which are excreted in the stool and the healthy kidney.^{3,11}

The ratio of carbohydrates to proteins is essential for nutrition. This

ratio will be reduced in the distal gut since carbohydrate is well fermented by gut distal microbiota. Individuals with the problem of slow gut transit (such as constipation) will have more growth of proteolytic bacteria, which can contribute to producing metabolic toxins and induce pro-inflammatory cytokines.³ Some individual factors, including gut acidity, antibiotics consumption, nutrient intake, psychological and physical stress, bowel wall edema, iron intake, genetics, and other diseases beyond the gastrointestinal problems could affect the gut microbiota balances, known as gut dysbiosis. These factors may further affect the overgrowth of the pathogenic bacteria, that can be translocated to the bloodstream.¹²⁻⁴

In healthy individuals, the gut barrier, including tight junction, enterocyte membranes, mucus, and gut wall immune system acts as a defense mechanism to prevent gut translocation, for instance, lumen materials or gut microbiota.¹⁵ The tight junction complex binds to the epithelial cells to prevent paracellular translocation. The tight junction consists of adhesive proteins such as occludin, claudin (the primary protective protein from solute and fluid diffusion), zonula occludent (ZO) protein, a cytosol protein, and actin and myosin peri junctional ring that regulate the paracellular permeability.^{3,15} The tight junction regulates its tightness based on physiological needs. It is the most efficient barrier against microbes, lipopolysaccharides, toxic fermentation products, digestive enzymes, and other potentially dangerous substances that can be translocated from the gut to the whole body. The gut immune system is essential in maintaining the dynamic balance between gut microbiota and host symbiosis. A balanced immune system is needed to preserve gut homeostasis, involving the good interaction between adaptive immunity, IgA, and T-cell regulator.^{3,15-17}

Table 1. Physiological effects of the gut microbiota.³

A. Gastrointestinal tract integrity and function
1. Tight junction protein structure restoration
2. Induction of epithelial heat-shock protein
3. Upregulation of mucin genes
4. Compete with the pathogen bacteria in binding with the gut epithelial cells
5. Secrete antimicrobial peptide
6. Suppress the gut inflammation
B. Effects in immune systems
1. Maturation of gut immune system
2. Decrease allergic response to food and environmental antigens
3. Increase immunomodulation and cell differentiation
C. Metabolic effects
1. Destroy indigestible polysaccharides
2. Help the absorption of complex carbohydrate
3. Vitamin K synthesis
4. Amino acids synthesis (threonine and lysine)
5. Biotransformation of conjugated bile acid
6. Food oxalate degradation

Gut dysbiosis in CKD

From the early stage of CKD, the gut microbiota changes quantitatively and qualitatively in its composition and metabolic activities. These changes may be due to the alteration in food transit time, lower protein absorption, decreased fiber intake, oral iron supplementation, and frequent antibiotic usage.^{3,6} Many factors affect CKD patients' longer colonic transit time, such as the dialysis modality, lifestyle, physical inactivity of the patient, phosphate binders, food restriction, fluid intake limitation, and other comorbid diseases such as diabetes, heart failure, and stroke. CKD patients are usually advised to restrict potassium intake, which means less intake of fruit and vegetables, which may further decrease fiber intake.^{3,18} In the uremic state, the digestion and the absorption of protein are disturbed and may increase the protein entering the colon, which consecutively is degraded by the proteolytic bacteria.^{3,19} Antibiotic usage

may also change the colonic microbiota.³ All these factors can contribute to inducing systemic inflammation and accumulate the uremic toxin, which is possible to translocate from the gut and excreted by the kidney. Inflammation and the uremic toxin play central roles in atherosclerosis and other complications of CKD.^{6,20}

Alteration in the gut barrier of CKD patients can lead to increase gut permeability. In uremia, gut barrier dysfunction is often found and manifested as endotoxemia without clinical infection. This is caused by the alteration of gut microbiota. Elevation of urea level and urease-producing bacteria will increase the ammonia in the gut lumen. This condition changes gut acidity and increases gut permeability by disrupting the tight junction of the enterocytes.^{6,15} Vaziri *et al.*¹⁵ showed a significant decrease of tight junction protein, claudin-1, occludin, and ZO-1, in the colon mucosal layer of CKD patients. It was related to the infiltration of mononuclear cells in

the lamina propria and increased the thickness of the colonic mucosa.¹⁵

CKD patients often experience edema and hypervolemia affecting the gut barrier dysfunction, especially ESKD patients who are on hemodialysis or peritoneal dialysis. In contrast, excessive ultrafiltration and hypotension during the hemodialysis will result in transient gut ischemia, and increases gut permeability and endotoxin translocation.¹⁵

Decreased pro-inflammatory cytokine clearance in CKD is related to oxidative stress and inflammation development. Inflammation is the most significant factor in the disease progression and CKD complications, such as cardiovascular disease, cachexia, and anemia. Oxidative stress and chronic inflammation stimulate NF- κ B, a transcription factor that regulates pro-inflammatory cytokines and chemokines. Increased gut barrier permeability in CKD may translocate bacterial products from the gut, which is proven by the DNA fragments of gut pathogens (both aerobic and anaerobic) in the circulation, whether they are at an earlier stage of CKD or on renal replacement therapy. These circulating bacterial products activate the innate immunity and induce CKD-related inflammation, which further increases cardiovascular disease and mortality.^{6,12,21}

Gut microbiota products are one of the important factors that can cause uremic toxin in CKD patients. The gut bacteria microbiota degrades almost 10 grams of protein to produce ammonia, thiol, phenol, and indole. Some fermentation products are excreted in stool, while others are absorbed and

excreted by the kidney. These products are found and accumulated in CKD patients. Phenols (p-cresol, p-cresyl sulfate (PCS), and p-cresyl glucuronide) and indole (indoxyl sulfate/IS) are the uremic toxins produced by the gut microbiota, which are bound to protein. P-cresol or PCS is the product of phenylalanine and tyrosine fermentation, while IS is the product of tryptophan fermentation.^{3,6,19,22}

The uremic toxin gives biological effects that can disturb other tissues. Both IS and PCS are related to fibrosis, decreased renal function, and disease progression. Indoxylsulfate is associated with endothelial injury, arterial stiffness, aorta calcification, profibrotic effects in the heart, cardiomyocyte hypertrophy, and predisposition factor of atrial fibrillation. In CKD patients with hemodialysis, PCS and IS are also related to peripheral vascular disease and venous access thrombosis.^{3,23-25} In a meta-analysis study reported that increased PCS and IS were associated with increased mortality in CKD patients, and increased PCS was also associated with an increased risk of cardiovascular events.²⁶

Anemia in CKD is related to the IS, which interferes with erythropoietin and induces the apoptosis of erythrocytes.^{27,28} Indoxyl Sulphate also decreases bone formation. It increases oxidative stress in the osteoblast, and further increases the resistance of parathyroid hormone, leading to the adynamic bone. There is a correlation between FGF-23 serum and IS. It marks the relationship between this molecule and metabolic bone disease in uremic patients.^{6,29,30}

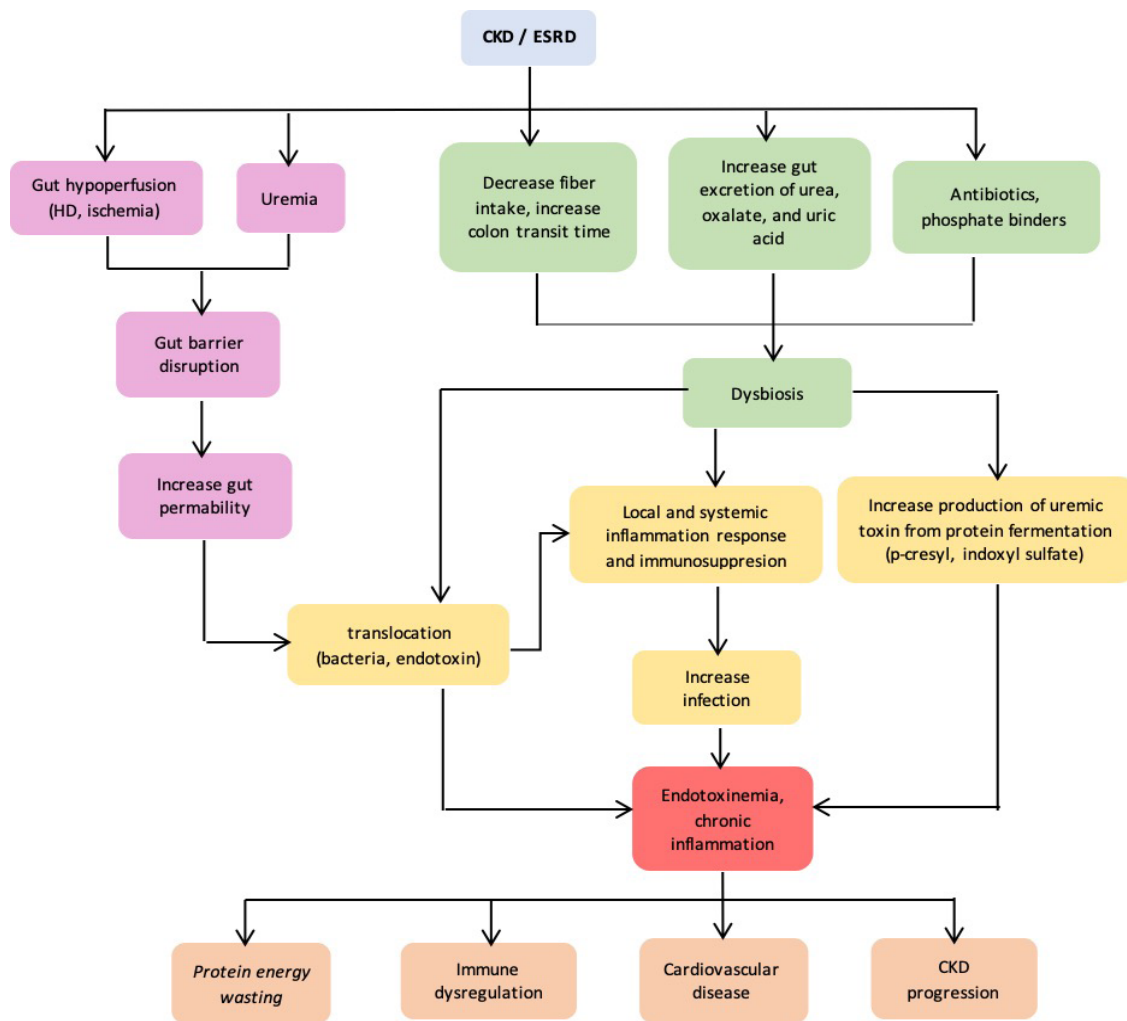


FIGURE 1. Relationship between uremia in CKD/ESKD on the gut barrier and microbiota. (Reproduced with permission from Sabatino, *et al.*)³

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Probiotic role in CKD

Several ways have been used to decrease uremic toxin, oxidative stress, and inflammation in CKD patients, including the restoration of gut microbiota balance. High-fibre diet increases the production of SCFA, the energy source of the gut microbiota, and it plays an important role in maintaining the function and integrity of gut mucosa. Fibre is used to lessen gut transit time, decreasing the time for amino acid fermentation. A low ratio of protein and fiber in the diet will bring benefits for CKD patients since the ratio correlates with the PCS and IS levels.^{31,32} A deficient protein diet (0.3 grams/kg body weight/day) combined with amino acid keto-analogue will decrease IS levels in CKD patients.^{33,34}

Uremic toxin production can be lowered by increasing saccharolytic bacteria which digest the fiber and decreasing proteolytic bacteria in the colon. Probiotic supplementation is given in CKD to decrease or excrete the uremic toxin by reducing the conversion of amino acid to PCS and IS. Probiotic is live microorganism which when administered in adequate amounts confer a health benefit on the host.^{12,35} The microorganism is modified genetically to produce some specific exogenous enzyme which can stand stomach acid and bile salt.^{12,35,36} It increases epithelial cell integrity. For instance, probiotics can inhibit the pathogen entry to epithelial cells and create a physical barrier and mucus by increasing the synthesis and secretion of mucin from goblet cells. Probiotics also protect gut integrity by inducing ZO-1 expression that can increase the intercellular tight junction between the gut epithelial cells.^{35,36}

Probiotics also decrease gut infection, especially the risk of *Clostridium difficile* infection in CKD patients. Some probiotic strains produce antibacterial substances, called

bacteriocin or antimicrobial peptides. *Lactobacillus* is capable of producing lactic acid that has an antimicrobial effect by reducing the local gut acidity.³⁵ Moreover, *Lactobacillus* also can induce and increase innate and adaptive immunity. Some probiotic strains help B cells differentiation and increase IgA production. Other strains stimulate the innate immune system by stimulating the dendritic cells, which then go to the mesenteric lymph nodes, inducing the T regulatory cell and producing the anti-inflammatory cytokines (IL-10 and TGF- β).³⁵ Wang *et al.*³⁷ conducted a study in ESKD patients with peritoneal dialysis who were supplemented by probiotics for 6 mo. It was found a significant decrease in endotoxin and pro-inflammatory cytokines (TNF- α and IL-6), and increased IL-10 with preservation of residual renal function.

Another study by Jia *et al.*³⁸ reported that probiotic supplementation decreased PCS in CKD and increased IL-6 levels. But, it did not affect serum creatinine, BUN, and hemoglobin levels. The increased level of IL-6 after probiotics supplementation is influenced by other factors, including the probiotic strain. IL-6 may act as pro- and anti-inflammatory cytokines, which is related to the signal transducers and activators of transcription (STAT) 1 and STAT 3 that activates and suppresses NF- κ B activity.^{38,39}

A study by Fagundes *et al.*⁴⁰ reported the health benefits of *Lactobacillus* and *Bifidobacterium* supplementation in CKD patients. They found a decrease in urea, BUN ammonia, plasma level of PCS, and IS in the group with probiotics supplementation. In addition, probiotics supplementation can increase the absolute number of *Bifidobacteria* population, both native and supplemented, which is beneficial in gut mucosal barrier function, decrease cytokine and endotoxin, and increase IL-10.^{40,41}

CONCLUSION

Gut dysbiosis leads to the elevation and the accumulation of absorbed uremic toxins, and later increases oxidative stress and chronic inflammation in CKD patients. Moreover, an increase in gut barrier permeability in CKD also elevates the amount of circulating endotoxin and promotes inflammation. Specific strain probiotic supplementation is an alternative that benefits CKD patients by slowing the disease progression and decreasing chronic inflammation.

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