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Review Article

Intestinal Dysbiosis and Targeted Strategies in Chronic Kidney Disease Patients

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Abstract

The human gut is home to approximately 100 trillion microbial cells, which live in a symbiotic coexistence with their host. Recently, the relationship between gut microbiota and Chronic Kidney Disease (CKD) has been receiving much attention. Recent studies have described that CKD could contribute to intestinal dysbiosis, that was associated with the progression of CKD and increased all-cause mortality. In this review, we discussed the role of gut microbiota in CKD and the possible targeted strategies.

Keywords: Chronic kidney disease; Gut microbiota; Intestinal dysbiosis; Targeted strategies

Introduction

The human gut is home to approximately 100 trillion microbial cells that constitute the gut ecosystem [1]. In health, gut microbiota lives in a symbiotic coexistence with their host and perform important physiological functions. Gut dysbiosis refers to an imbalanced intestinal microbial community with quantitative and qualitative changes in the composition and metabolic activities of the gut microbiota [2]. Gut dysbiosis may contribute to many chronic disease, such as: Chronic kidney disease (CKD), obesity, diabetes mellitus, cancer, inflammatory bowel disease and liver cirrhosis [3]. CKD is a global health problem, affecting 6%-10% of the adult population [4]. End stage renal disease (ESRD) patients required renal replacement therapy and the number of them increases 10%-15% per year [5]. In recent years, the intestinal dysbiosis are observed in CKD/ESRD patients, that may contribute to CKD progression and complications [4,6]. On this basis, several strategies have been investigated to reestablishing symbiosis, aimed to prevent CKD progression and increased cardiovascular risk. In this review, we discussed the role of gut microbiota in CKD and the possible targeted strategies.

Gut Ecosystem in Health and in CKD/ESRD Patients

The gut microbiota includes bacteria, archaea, fungi, protozoa and viruses. In recent years, most studies focused on bacteria. In health, gut microbiota is constituted by more than 50 bacterial phyla [7] with Bacteroidetes and Firmicutes contributing to > 90% of all species The complex community of microbiota including probiotics and potentially pathogenic bacteria in the gut constitutes a dynamic and symbiotic ecosystem interaction with their host, which influences the physiology, nutrition, metabolism and immune function. In diseases, the equilibrium between the host and the gut microbiota is altered. Relevant quantitative and qualitative changes in gut microbiota have been demonstrated in CKD/ESRD patients [4]. Gathering the information from human patients and animal models, CKD is associated with lower levels of the families *Enterobacteriaceae (Escherichia* spp.*, Enterobacter* spp.*, Klebsiella* spp.*, Proteus* spp.*), Lachnospiraceae, Ruminococcaceae* and with higher levels of families *Bifidobacteriaceae (Bifidobacterium* spp.*), Lactobacillaceae (Lactobacillus* spp.), *Bacteroidaceae, Prevotellaceae* [4,8-10]. Uremic toxins are now considered important factors in the pathogenesis of altering intestinal milieu and function of the gut microbiome. Increased secretion of urea

and uric acid into the gut can increase pH leading to mucosal damage, irritation and intestinal dysbiosis [3,4]. Bacterial families possessing urease, uricase, p-cresol and indole-forming enzymes are expanded, as well as the short-chain fatty acid (SCFA)-forming bacteria are contracted [11]. SCFAs is one of the important end products of carbohydrates (CHO) that could protect kidney [7]. Patients with CKD/ESRD often have a low intake of dietary fiber - fruits and vegetables to restricting potassium intake. CHO and proteins are two usual substrates of gut microbiota. The limited fiber diet could decrease the saccharolytic bacteria and increase the proteolytic bacteria. In addition, CKD patients may have impaired protein digestion and absorption that increasing the available undigested proteins for proteolytic bacteria. Furthermore, the slower gastrointestinal transit time caused by limited intake of dietary fiber, the frequent use of antibiotics or phorsphate binders may worsen constipation that leading to dysbiosis in CKD/ESRD patients.

Intestinal Dysbiosis and Uremic Toxin

A large number of compounds excreted by kidney accumulate in CKD patients, especially in its most advanced stages. Uremic solutes can interfere with many biological activities and are called uremic toxins. They are classified into 3 groups according to their physicochemical characteristics: small water-soluble, middle molecules and protein-bound uremic solutes [12]. In recent years, Protein-bound uremic toxins (PBUTs) have been receiving much attention because of their effects on cardiovascular disease risk and their incomplete clearance by dialysis [4]. The precursors of PBUTs are formed during protein fermentation by gut microbiota. At present, some uremic toxins have been extensively studied. Indoxyl sulphate (IS) Dietary tryptophan are converted into indole by gut microbiota. After absorbed by the intestines, indole is metabolized into IS by liver. In health, IS is mainly excreted by the kidney. Whereas the increased blood level of IS levels is significantly associated with the decline in renal function [13]. IS is a predictor of CKD progression, all-cause and cardiovascular mortality [14-16]. It can mediate expression of genes regulating inflammation and fibrosis related to renal fibrosis, cardiac fibrosis and atherosclerosis, such as IL-1β, IL-6, TNF-α, TGF-β, PAI-1 [12]. Ichii O et al. proposed that IS could contribute to progressive glomerular injury by increasing the activity of the Aryl hydrocarbon receptor (AhR) in podocyte [17]. In addition, IS can promote interstitial fibrosis and glomerulosclerosis by activing the intrarenal Renine-angiotensine- aldosterone system (RAAS). Barreto et al. showed that an elevated level of IS was associated with vascular stiffness and aortic calcification [16].

P-cresol sulfate (PCS)

Breakdown of phenylalanine and tyrosine by gut microbiota generates p-cresol. P-cresol are metabolized into PCS by liver after absorbed. PCS levels increased with decreasing estimated glomerular filtration rate (eGFR) [13] PCS was implicated in the development of renal inflammation and fibrosis and it can also active the intrarenal RAAS, promote interstitial fibrosis and glomerulosclerosis [18].In addition, the serum levels of PCS were associated with the mortality in hemodialysis patients [19] and were an independent predictor for cardiovascular events [7]. Han et al. demonstrated that PCS could induce NADPH oxidase activity and reactive oxygen species production facilitating cardiac apoptosis and resulting in diastolic dysfunction [20]. Both IS and PCS could decreased the expression of the renal Klotho gene resulting to cellular senescence.

Trimethylamine N-oxide (TMAO)

Trimethylamine N-oxide (TMAO) is another uremic toxin produced by the gut microbiota that has been studied in recent years. TMAO, a gut microbial-dependent metabolite of dietary choline, phosphatidylcholine and L-carnitine, is elevated in CKD patients. In animal model studies, dietary exposure to either choline or TMAO both lead to development of renal tubulointerstitial fibrosis and early measures of dysfunction (cystatin C) [21]. TMAO directly contributes to progressive renal fibrosis and dysfunction. Missailidis et al. found TMAO levels correlated with increased systemic inflammation are an independent predictor of mortality in CKD 3–5 patients [22]. In addition, several reports demonstrate that higher TMAO levels are associated with cardiovascular disease and heart failure [23].

Other uremic toxin

Moreover, other microbial related uremic solutes are also harmful to human, such as guanidine, hippurate, and phenylacetylglutamine. Guanidine is produced by creatinine by *Pseudomonas stutzeri*. In animal studies, Guanidine accumulation in CKD could increase mortality [24]. Hippurate can cause anion gap acidosis in CKD. Phenylacetylglutamine may contribute to tubular damage and progression of CKD mediated by phenyl acetic acid. The mechanism of uremic toxins need more researches in future [4].

Bacteric Translocation and Inflammation

The intestinal epithelium is a single layer of columnar epithelial cells which are bound together by tight junctions to prevent bacteria and harmful substances entering from intestines. In recent studies, the relationship between uremia and the impaired intestinal barrier function has been reported [25-28]. A marked depletion of the constituents of colonic epithelial tight junction (claudin-1, occluding and ZO1) have been associated with increased intestinal permeability in uremic mice and *in vitro* studies [26,27], resulting in increased permeability and epithelial barrier dysfunction [4]. The impairment of intestinal barrier function lead

to translocation of bacteria and endotoxin across the intestinal wall. And the translocation of bacteria and their components could cause a potentially harmful pro-inflammatory response to clear the invading microbes by the intestinal and systemic immune system. The response includes the secretion of interleukin-1 (IL-1) and IL-6 from intestinal epithelial cells, the promotion of TH1 and TH17 response by dendritic cells and macrophages, the production of higher levels of commensal- specific IgG by B cells [4,8]. Endotoxin, the hydrophobic anchor of lipopolysaccharides (LPS) from Gram-negative bacteria cell membranes, could cause inflammatory response when it was exposed. LPS binding to its receptor complex on macrophages results in increased production of inflammatory cytokines, such as interferon-β(IFN-β), IFN-γ, IL-1β, IL-6, tumor necrosis factor-α(TNF- α) and IL-12. Plasma levels of sCD14, the soluble receptor of endotoxin, were considered an independent predictor of mortality in ESRD patients [29]. Endotoxemia in CKD patients was associated with systemic inflammation resulting in CKD progression and atherogenesis [4].

Targeted Strategies of Intestinal Dysbiosis in CKD/ESRD

Understanding the role of intestinal dysbiosis in the pathogenesis of CKD may lead to explore new strategies to reestablishing symbiosis, aimed to prevent CKD progression and increased cardiovascular risk. Several strategies have been investigated in animal models or human with CKD.

Probiotics

Probiotics consists of live bacteria for health benefit on the host, such as: *Bifidobacteria, Lactobacilli* and *Streptococci.* A recent study showed that frequent use of yogurt and/or probiotics is associated with decreased odds of proteinuric kidney disease [30]. Miranda Alatriste PV et al. found that the serum urea concentrations is > 10% decrease in patients with stage 3 and stage 4 CKD after a treatment with *Lactobacillus casei* Shirota [31]. Probiotics could significantly reduce the serum levels of endotoxin and pro-inflammatory cytokines (TNF-αand IL-6), IL-5, increase the serum levels of anti-inflammatory cytokine (IL-10) and preserve residual renal function in peritoneal dialysis patients [32]. In addition, treatment with *L. acidophilus* ATCC-4356 could reduce the atherosclerotic burden in ApoE -/- mice [33].

Prebiotics is a substrate that is selectively utilized by host microorganisms conferring a health benefit [34]. Prebiotics promotes the growth of *Bifidobacteria* and *Lactobacilli* species in the gut to stabilizing the intestinal barrier function and reducing the abundance of pathogenic bacteria [4]. Galacto-oligoaccharides could decrease cecal indole and serum IS, attenuate renal injury and modified the gut microbiota in the Nx rats [35]. The prebiotic oligofructose-inulin significantly reduced PCS generation rates and serum concentrations in hemodialysis patients [36]. Increasing fiber intake in CKD patients may reduce serum creatinine levels and improve eGFR [37].

Synbiotics

Synbiotic is the combination of probiotics and prebiotics. Treatment with the synbiotic in patients with CKD resulted in significant reduction of serum PCS [38]. In a recent randomized trial, Rossi et al demonstrated that synbiotics didn't significantly reduce serum IS but did decrease serum PCS and favorably modified the stool microbiome, particularly with enrichment of *Bifidobacterium* and depletion of *Ruminococcaceae* in CKD patients [39].

High-fiber diet

Krishnamurthy VMR et al. suggest that high dietary total fiber intake is associated with decreased inflammation and all-cause mortality in CKD patients [40]. In an animal study, high resistant starch diet could delay the progression of CKD and attenuate oxidative stress and inflammation [41]. Each 10 g/day increase in total dietary fiber intake was related to a 17% lower mortality risk [4], However, CKD/ESRD patients often have a low intake of dietary fiber to restricting potassium intake. In currently, the benefit amount for dietary fiber in CKD/ ESRD patients is still not clear and more research is needed in future [4].

Sorbents

AST-120 is an orally ingested intestinal spherical carbon adsorbent that can adsorb various compounds, including indole, p-cresol and other toxins in the gut [4]. Administration of AST-120 attenuated the disruption of colonic epithelial tight-junction and the associated endotoxemia, oxidative stress and inflammation in animal study [42]. AST-120 could lower serum IS levels and improve renal function [6,43]. A prospective randomized study has demonstrated that AST-120 was associated with reducing the progression of CKD in mild-to-moderate patients [44]. But in a recent randomized placebo-controlled EPPIC trial, no benefit was observed in adding AST-120 to standard therapy in patients with moderate to severe CKD [45].

Laxatives

CKD patients often suffer from constipation, which can lead to excessive production of uremic toxins. A chloride-channel activator - lubiprostone can be used for chronic constipation. In recent study, Mishima E found that lubiprostone could ameliorate the progression of CKD by improving the gut environment and reducing uremic toxins in uremic mice [46]. Clinical studies are needed in future.

Other strategies

Other strategies were also described to reestablishing symbiosis, such as: sevelamer, acarbose, Hemo-Filtrate-Reinfusion (HFR), fecal microbiota transplantation (FMT) The noncalcium phosphate binder sevelamer is associated with a significant decrease in hs-C reactive protein, IL-6, serum endotoxin levels and sCD14 concentrations in hemodialysis patients [47]. Phan O et al. demonstrated that sevelamer delays not only vascular calcification but also atherosclerotic lesion progression in uremic apolipoprotein E-deficient mice [48]. However, the decreased serum concentrations of indoxyl sulphate and p-cresyl were not observed in animal models and in dialysis patients [4]. Acarbose is a group of inhibitors of α-glucosidase enzymes in the intestinal brush border. The treatment with acarbose could lower the generation of p-cresol and decrease its serum concentrations [49].

HFR is a new dialysis technique that combines the processes of diffusion, convection and adsorption. As we know, Hemodialysis (HD) and hemodiafiltration couldn't clear p-cresol and IL-6 effectively from the plasma. In the recent study, total plasma p-cresol levels were reduced by HFR obviously [50]. FMT is accepted as an effective intervention to restoring the microbiota dysbiosis [6,51]. Transplantation of a rich pool of exogenous bacteria to rats leads to an increase in bacterial diversity [4]. Recently, no large studies have been confirmed the effect of FMT on restoring the gut microbiota in CKD patients. More animal and clinical studies are needed in future [52].

Conclusion

The gut microbiota lives in a symbiotic coexistence with their host, constituted a complex micro-ecosystem. Recent studies have described that CKD could contribute to intestinal dysbiosis and intestinal dysbiosis was associated with the progression of CKD and increased all-cause mortality [1,46]. Until recently, the exact mechanism of gut microbiota associated with CKD progression is still not clear. Advances in sequencing techniques, bioinformatics and metabolomics may expand our understanding of the role of gut microbiota in CKD patients [1]. In future, more new strategies will be explored to reestablishing symbiosis to preventing the progression of CKD progression and increased cardiovascular risk.

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