SOHAG MEDICAL JOURNAL
Vol. 22 No.1 Jan 2018

Gut microbiome in chronic kidney disease

Noher Mohammad Abass

Department of Internal Medicine, Sohag Faculty of Medicine, Sohag University

Overview

Normal gut microbiota influences the well-being of the host by contributing to its nutrition, metabolism, physiology, and immune function [1]. Disturbance of normal gut microbiota (dysbiosis) has been implicated in the pathogenesis of diverse illnesses such as obesity [2], type 2 diabetes [3], inflammatory bowel disease [4] and cardio vascular disease [5]. Quantitative and qualitative alterations in gut microbiota are noted in patients with CKD and ESRD [6].

Factors that modulate the gut microbiome

The gut microbiome is relatively stable, but adapts dynamically to changing environment and health. De Filippo and colleagues investigated the long-term effect of dietary pattern by comparing the faecal microbiota of Caucasian children and children in rural Africa, where the diet is plant based and high in fiber content [7]. African children showed a significant enrichment of Bacteroidetes and a depletion of Firmicutes when compared with the European children. In addition, the bacteria present in the African children expressed genes related to cellulose and xylan hydrolysis. These results illustrate that these bacteria co-evolved with the polysaccharide-rich diet in Africans, which allowed them to maximize the energy intake from fibers [7].

Antibiotics can have a profound effect on the gut microbiome. For example, ciprofloxacin treatment results in a profound and rapid loss of diversity and richness of the microbiome, with a shift in the community composition as early as 3–4 days after drug initiation**.** One week after stopping antibiotics, the microbial communities began to return to their initial state, but the recovery was often incomplete [8].

The composition of gut microbiota is also influenced by the host genetics and immune status [9].

In health, the gut microbiome exists in 'symbiosis', a state of coexistence in mutual harmony, which is disturbed in disease states. A number of interesting and provocative associations between disease and microbiome are emerging, which remains to be confirmed [10]. Patients with progressive IgA nephropathy have a distinct microbiome profile, with higher percentages of some genera/species of Ruminococcaceae, Lachnospiraceae, Eubacteriaceae and Streptococcaeae[11]. The microbiome has also been implicated in kidney stone formation [12]. The gut microbiome can also produce beneficial metabolites, such as short-chain fatty acids (SCFAs) that could be kidney protective [13].

Gut Microbiome in Chronic Kidney Disease

The microbiome profile is altered in patients with CKD and in patients with end-stage renal disease (ESRD). As many as 190 microbial units differed significantly in abundance when the gut microbiome of ESRD patients was compared to that of apparently healthy controls [14]. In another study, the number of aerobic bacteria, including Enterobacteria and Enterococci species was shown to be higher in ESRD patients than in controls . Among anaerobic bacteria, hemodialysis patients had significantly higher counts

for Clostridium perfringens and lower numbers of Bifidobacterium species [15].

Mechanism of dysbiosis in chronic kidney disease

Dysbiosis is an imbalance in the intestinal microbiota that precipitates changes in the usual activities of gastrointestinal tract, resulting in production of toxins and deleterious effects in the organism [16]. Several factors contribute to dysbiosis in patients with CKD, such as slowing of intestinal transit, decreases in digestive capacity and secretion of ammonia and urea into the gut [17]. The cause of slow colonic transit time and frequent constipation observed in CKD and particularly hemodialysis patients seems to be multifactorial. Dietary restriction and low fiber consumption, lack of activity, use of phosphate binders and co-morbidities such as diabetes and heart disease might all contribute to the greater prevalence of constipation in these patients [18].

Slowing of the intestinal transit permits proliferation of bacteria. Impaired protein digestion results in undigested protein being delivered to the colon, which also causes proliferation of proteolytic bacteria. There is a minimal increase in the serum concentration of uric acid in advanced CKD owing to CKD-induced adaptive secretion of uric acid by the colon [19]. As a result of the urea/uric acid secretion in the gut, bacterial families possessing urease, uricase, phenol and indole-forming enzymes are expanded, whereas the SCFA-forming bacteria are contracted in ESRD patients [20].

Furthermore, increased secretion of ammonia and urea into the gut changes the pH, leading to the growth of pH-sensitive bacteria, ESRD disease patients also have changes in diet, including a decrease in fiber intake, which decreases the bifidobacteria. Finally, frequent use of antibiotics and iron delivered in either oral or intravenous form could alter the microbial landscape in the gut [20].

Clinical Consequences of Intestinal Dysbiosis

Gut microbiota plays an important role in regulating immunity and host metabolism. Consequently, disruption of the gut microbiota has been associated with various human diseases of the immune system, gastrointestinal tract, and cardiovascular system. Both CKD and ESRD are associated with altered gut microbiome **[21]**. In patients with chronic renal failure, uremia has been shown to increase intestinal permeability, which together with loss of barrier function, lead to entry of live bacteria, endotoxin molecules, and gut derived uremic toxins into the systemic circulation . This results to a persistent systemic inflammation that over time will drive endothelial dysfunction, atherogenesis, and CVD [22].

A number of gut bacteria and their products are now known to be associated with CVD identified Chryseomonas, Veillonella, and Streptococcus in atherosclerotic plaques [23]. Elevated endotoxin level has also been shown to be a strong risk factor for the development of atherosclerosis in the general population [24]. CVD and mortality in patients with CKD and hemodialysis patients is associated with elevated plasma level of sCD14 (the receptor for endotoxin) [25]. Furthermore, elevated levels of indoxyl sulfate and p-cresol sulfate, two of the uremic toxins generated by gut microbes, have been associated with risk of cardiovascular mortality in patients with chronic renal failure [26].

Recent studies have revealed trimethylamine N-oxide (TMAO), choline, and betaine to be associated with heart disease **[27]**. TMAO is

formed in the liver from the metabolism of trimethylamine gas, a product of choline catabolism by the intestinal microbiota. TMAO is also produced from dietary carnitine, which is high in red meat and serves as another substrate for gut flora to produce TMAO [28].Elevated TMAO level predicted an increased risk of major adverse cardiovascular events in a study involving 4007 patients undergoing elective coronary angiography [29].

More recently, gut microbiome dysbiosis has been associated with essential hypertension which is considered another causative factor for chronic renal failure. The potential role of the microbiome in regulating human BP and causing hypertension is mostly based on animal studies. One of the few human studies that looked at gut microbiome and hypertension was the gut microbiome composition analysis of patients with elevated systolic blood pressure (SBP) compared with those with normal SBP. Results of this study revealed a decreased bacterial richness and altered bacterial compositions in patients with elevated SBP [30] .

The gut microbiota can ferment dietary fibers to yield SCFAs acetate and propionate (produced by Bacteroidetes phylum members) as well as butyrate (produced by bacteria of the Firmicutes phylum) [31]. In addition to their ability to moderate immune signaling [32] and anti-inflammatory impact on both colonic epithelium and immune cells [33], SCFAs also have a vasodilation property in vitro as both butyrate and propionate can induce dilation of human colonic arteries [34]. Interestingly, the SCFA olfactory receptor 78 (Olfr78) is expressed in the kidneys and regulates BP, as shown by BP reduction of about 20 mmHg following administration of propionate to normal mice [35].

Targeted interventions to treat intestinal dysbiosis in CKD

Modulation of Gut Microbiota:

Prebiotics

A prebiotic is a non-digestible (by the host) food ingredient that has a beneficial effect through its selective stimulation of the growth or activity of one or a limited number of bacteria in the colon [36]. The candidate prebiotics include inulin, fructo-oligosaccharides,galacto-oligosaccharides,soya-oligosaccharides,xylo-oligosaccharides, and pyrodextrins. Prebiotics promote the growth of Bifidobacteria and Lactobacilli species at the expense of other groups of bacteria in the gut, such as Bacteroides species, Clostridia species, and enterobacteria[37]. Preliminary evidence indicates that prebiotic oligofructose-enriched inulin (p-inulin) promotes growth of Bifidobacteria species, mediates weight loss, reduces inflammation, and improves metabolic function [38]. Several studies reported that serum concentrations of p-cresol and indoxyl sulfate are reduced by the oral intake of p-inulin in hemodialysis patients[39]

Probiotics

Probiotics are defined by the United Nations' Food and Agriculture Organization and the World Health Organization as "live microorganisms" that when administered in adequate amounts confer a health benefit on the host [40]. Probiotics consist of living bacteria, such as Bifidobacteria species, lactobacilli, and streptococci, that can alter gut microbiota and affect the inflammatory state. Hemodialysis patients treated with oral Lactobacillus acidophilus showed decreased serum dimethylamine, a potential uremic toxin [40].

Acarbose

Acarbose is an inhibitor of a-glucosidase enzymes in the intestinal brush-border that blocks the hydrolysis of poly- and oligosaccharides to glucose and other monosaccharides. The undigested oligosaccharides that enter the colon act as fermentable carbohydrates showed that treatment with acarbose reduces the colonic generation of p-cresol in healthy persons [42].

Gut Microbiome Transplantation

Transplantation of a rich pool of exogenous bacteria led to an increase in bacterial diversity and changing the microbiome of the recipients to resemble that of the donor [4

References

1. **Bäckhed F, Ley RE, Sonnenburg JL,Peterson DA, Gordon JI**: Host-bacterial utualism in the human intestine. Science 2005; 307: 1915–1920.
2. **Ley RE, Turnbaugh PJ, Klein S, Gordon JI**: Microbial ecology: Human gut microbes associated with obesity. Nature 2006; 444: 1022–1023.
3. **Qin J, Li Y, Cai Z, Li S, Zhu J, Zhang F, Liang S, ZhangW, Guan Y**: Ametagenome-wide association study of gut microbiota in type 2 diabetes. Nature 2012; 490: 55–60.
4. **Frank DN, St Amand AL, Feldman RA, Boedeker EC, Harpaz N, Pace NR:** Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. Proc Natl Acad Sci US A 2007; 104: 13780–13785.
5. **Wang Z, Klipfell E, Bennett BJ, Koeth R, Levison BS, Dugar B, Feldstein AE, Britt EB, Fu X, Chung YM,WuY, Schauer P, Smith JD, Allayee H, TangWH, Di Donato JA, Lusis AJ, Hazen SL**: Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. Nature 2011; 472: 57–63
6. **Vaziri ND,Wong J, Pahl M, Piceno YM, Yuan J, De Santis TZ, Ni Z, Nguyen TH, Andersen GL**: Chronic kidney disease alters intestinal microbial flora. Kidney Int 2013; 83: 308–315.
7. **De Felippo C, Cavalieri D, Di Paola M, Ramazzotti M, Poullet JB, Massart S, Collini S, Pieraccini G & Lionetti P :** Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. Proc Natl Acad Sci USA 2010; 107, 14691–14696.
8. **Dethlefsen L & Relman DA** : Incomplete recovery and individualized responses of the human distal gut microbiota to repeated antibiotic perturbation. Proc Natl Acad Sci USA 2011; 108 Suppl 1 , 4554–4561.
9. **Goodrich JK,Waters JL, Poole AC, Sutter JL, Koren O, Blekhman R, Beaumont M, Van Treuren W, Knight R, Bell JT, Spector TD, Clark AG & Ley RE** : Human genetics shape the gut microbiome. Cell 2014; 159, 789–799.
10. **Amar J, Lange C, Payros G, Garret C, Chabo C, Lantieri O, Courtney M, Marre M, harles MA, Balkau B & Burcelin R :** Blood microbiota dysbiosis is associated with the onset of cardiovascular events in a large general population: the D.E.S.I.R. study. PLoS One 2013; 8: e54461.
11. **De Angelis M, Montemurno E, Piccolo M, Vannini L, Lauriero G, Maranzano V, Gozzi G, Serrazanetti D, Dalfino G, Gobbetti M & Gesualdo L :**Microbiota and metabolome associated with

immunoglobulin A nephropathy (IgAN). PLoS One 2014;9: e99006.

12. **Zheng X, Zhao A, Xie G, Chi Y, Zhao L, Li H,Wang C, Bao Y, JiaW, Luther M, Su , Nicholson JK & JiaW:** Melamine-induced renal toxicity is mediated by the gut microbiota. Sci Transl Med 2013;5: 172- 22.

13. **Andrade-Oliveira V, Amano MT, Correa-Costa M, Castoldi A, Felizardo RJ, de Almeida DC, Bassi EJ, Moraes-Vieira PM, Hiyane MI, Rodas AC, Peron JP, Aguiar CF, Reis MA, Ribeiro WR, Valduga CJ, Curi R, Vinolo MA, Ferreira CM& Cˆamara NO :** Gut bacteria products prevent AKI induced by ischemia–reperfusion. J Am Soc Nephrol 2015;26: 1877–1888.

14. **Vaziri ND,Wong J, Pahl M, Piceno YM, Yuan J, Desantis TZ:** Chronic kidney disease alters intestinal microbial flora. Kidney Int.2013; 83(2):308–15.

15. **Hida M, Aiba Y, Sawamura S, Suzuki N, Satoh T**: Inhibition of the accumulation of uremic toxins in the blood and their precursors in the feces after oral administration of Lebenin, a lactic acid bacteria preparation, to uremic patients undergoing hemodialysis. Nephron. 1996;74(2):349–55.

16. **Schepers E, Glorieux G, Vanholder R**: The gut: the forgotten organ in uremia? Blood Purif. 2010;29(2):130–6.

17. **Ramezani A & Raj DS :** The gut microbiome, kidney disease, and targeted interventions. J Am Soc Nephrol 2014; 25: 657–670.

18. **Wu MJ, Chang CS, Cheng CH, Chen CH, LeeWC, Hsu YH, Shu KH & Tang MJ :** Colonic transit time in long-term dialysis patients. Am J Kidney Dis 2004; 44: 322–327.

19. **Alderman MH, Cohen H, Madhavan S & Kivlighn S :** Serum uric acid and cardiovascular events in successfullytreated hypertensive patients. Hypertension 1999; 34:144–150.

20. **Wong J, Piceno YM, DeSantis TZ, Pahl M, Andersen GL & Vaziri ND :** Expansion of urease- and uricase-containing, indole- and p-cresol-forming and contraction of short-chain fatty acid-producing intestinal microbiota in ESRD. Am J Nephrol 2014;39: 230–237.

21. **Ramezani A,Massy ZA, Meijers B, Evenepoel P, Vanholder R, Raj DS**: Role of the gut microbiome in uremia: a potential therapeutic target. Am J Kidney Dis. 2016; 67(3):483–98.

22. **Carrero JJ, Stenvinkel P**: Inflammation in end-stage renal disease- what have we learned in 10 years? Semin Dial. 2010; 23(5):498–509.

23. **Koren O, Spor A, Felin J, Fak F, Stombaugh J, Tremaroli V:**Human oral, gut, and plaque microbiota in patients with atherosclerosis. Proc Natl Acad Sci U S A. 2011;108(Suppl 1):4592–8.

24. **Wiedermann CJ, Kiechl S, Dunzendorfer S, Schratzberger P, EggerG, Oberhollenzer F:** Association of endotoxemia with carotid atherosclerosis and cardiovascular disease: prospective results from the Bruneck Study. J Am Coll Cardiol. 1999; 34(7):1975–81.

25. **Poesen Rl, Ramezani A, Claes K, Augustijns P, Kuypers D, Barrows :** Associations of soluble CD14 and endotoxin with mortality, cardiovascular disease, and progression of kidney disease among patients with chronic kidney disease. CJASN. 2015; In Press.

26. **Lin CJ,Wu V,Wu PC,Wu CJ :** Meta-analysis of the associations of p-cresyl sulfate (PCS) and indoxyl sulfate (IS) with cardiovascular events and all-cause mortality in patients with chronic renal failure . PLoS One. 2015;10(7):e0132589.

27. **Velasquez MT, Ramezani A, Manal A, Raj DS:**Trimethylamine NOxide:The Good, the Bad and the Unknown. Toxins (Basel). 2016; 8(11).

28. **Tang WH, Wang Z, Kennedy DJ, Wu Y, Buffa JA, Agatisa-Boyle B**: Gut

microbiota-dependent trimethylamine N-oxide (TMAO) pathway contributes to both development of renal insufficiency and mortality risk in chronic kidney disease. Circ Res. 2015;116(3):448–55.

29. **Tang WH, Wang Z, Fan Y, Levison B, Hazen JE, Donahue LM:** Prognostic value of elevated levels of intestinal microbegenerated metabolite trimethylamine-N-oxide in patients with heart failure: refining the gut hypothesis. J Am Coll Cardiol. 2014; 64(18):1908–14.

30. **Yang T, Santisteban MM, Rodriguez V, Li E, Ahmari N, Carvajal JM:** Gut dysbiosis is linked to hypertension. Hypertension. 2015; 65(6):1331–40.

31. **Macfarlane S, Macfarlane GT**: Regulation of short-chain fatty acid production. Proc Nutr Soc. 2003; 62(1):67–72.

32. **Le PE, Loison C, Struyf S, Springael JY, annoy V, DecobecqME:** Functional characterization of human receptors for short chain fatty acids and their role in polymorphonuclear cell activation. J Biol Chem. 2003; 278(28):25481–9.

33. **Round JL, Mazmanian SK:**The gut microbiota shapes intestinal immune responses during health and disease. Nat Rev Immunol. 2009; 9(5):313–23.

34. **Mortensen FV, Nielsen H,MulvanyMJ, Hessov I**: Short chain fatty acids dilate isolated human colonic resistance arteries. Gut. 1990; 31(12):1391–4.

35. **Pluznick JL, Zou DJ, Zhang X, Yan Q, Rodriguez-Gil DJ, Eisner C et al:** Functional expression of the olfactory signaling system in the kidney. Proc Natl Acad Sci U S A 2009; 106(6):2059–2064.

36. **Gibson GR, Probert HM, Loo JV, Rastall RA, Roberfroid MB**: Dietary modulation of the human colonic microbiota: Updating the concept of prebiotics. Nutr Res Rev 2004; 17: 259–275.

37. **Silk DB, Davis A, Vulevic J, Tzortzis G, Gibson GR**: Clinical trial: the effects of a trans-galactooligosaccharide prebiotic on faecal microbiota and symptoms in irritabl bowel syndrome. Aliment Pharmacol Ther 2009; 29: 508–518.

38. **Cani PD, Neyrinck AM, Fava F, Knauf C, Burcelin RG, Tuohy KM,GibsonGR, elzenne NM:** Selective increases of bifidobacteria in gut microflora improve high-fat-diet-induced diabetes in mice through a mechanism associated with endotoxaemia. Diabetologia 2007; 50: 2374–2383.

39. **Krishnamurthy VM, WeiG, Baird BC,Murtaugh M, Chonchol MB, Raphael KL, Greene T, Beddhu S:** High dietary fiber intake is associated with decreased inflammation and all cause mortality in patients with chronic kidney disease. Kidney Int 2012; 81: 300–306.

40. **Food and Agriculture Organization of the United Nations (FAO).** Health and nutritional properties of probiotics in food including powder milk with live lactic acid bacteria. Available at: Accessed October 30, 2013.

41. **van Baarlen P, Troost FJ, van Hemert S, vander Meer C, de Vos WM, de Groot PJ, Hooiveld GJ, Brummer RJ, Kleerebezem M; van BP**: Differential NF-kappaB pathways induction by Lactobacillus plantarum in the duodenum of healthy humans correlating with immune tolerance. Proc Natl Acad Sci U S A 2009; 106: 2371–2376.

42. **Evenepoel P, Bammens B, Verbeke K,Vanrenterghem Y**: Acarbose treatmentlowers generation and serum concentrations of the protein-bound solute p-cresol: a pilot study. Kidney Int 2006; 70: 192–198.

43. **Persky SE, Brandt LJ**: Treatment of recurrent Clostridium difficile-associated diarrhea by administration of donated stool directly through a colonoscope. Am J Gastroenterol 2000; 95: 3283–3285.