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From intestine to kidney; a narrative literature review

Hamid Nasri[1], Azar Baradaran[2], Parto Nasri[1], Marzieh Kafeshani[3], Shervin Assari[4,5], Mahmoud Rafieian-Kopaei[6*]

[1]Department of Nephrology, Isfahan University of Medical Sciences, Isfahan, Iran
[2]Department of pathology, Isfahan University of Medical Sciences, Isfahan, Iran
[3]Food Security Research Center, Department of Clinical Nutrition/Community Nutrition/Food Science and Technology, School of Nutrition and Food Science, Isfahan University of Medical Sciences, Isfahan, Iran
[4]Department of Psychiatry, School of Medicine, University of Michigan, Ann Arbor, MI, USA
[5]Center for Research on Ethnicity, Culture and Health, School of Public Health, University of Michigan, Ann Arbor, MI, USA
[6]Medical Plants Research Center, Shahrekord University of Medical Sciences, Shahrekord, Iran

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ABSTRACT

Chronic renal failure results to a systemic inflammation and oxidative stress which play a key role in chronic renal failure progression and its unfavorable consequences. Various factors including oxidative stress, metabolic acidosis, decreased clearance of pro-inflammatory cytokines, obesity, infections and dialysis access problems contribute to micro-inflammation in chronic renal failure or hemodialysis. Recently much attention has been directed toward, the possible association between the alterations in gut microbiota composition and intestinal barrier which detected to aggravate inflammation and oxidative stress in chronic renal failure patients. In fact, integrity of the gastrointestinal epithelial cell tight junction that, seals the gap of the epithelial cells is essential to prevent the entrance of antigens, microbial toxins and other harmful luminal contents into the submucosal area and eventually in the body's internal environment. Inflammation is a continuous aspect and is a main mediator of the progression of chronic renal failure and its several complications, such as cardiovascular complications. Renal failure results in disintegration of the colonic tight junction system, a phenomenon, which can attribute to the systemic inflammation and account for the previously established evidence of defective intestinal barrier function in uremic subjects. Several factors can affect gut microbiota composition such as exercise, smoking, and diet including macronutrient, polyphenol, fiber, vitamins. Thus, life-style interventions that promote healthy diet and physical activity are important strategies to prevent inflammatory diseases, including progression of renal failure. Further studies including randomized controlled trials seem necessary in this field.

Review

Core tip: Chronic renal failure results to a systemic inflammation and oxidative stress which play a key role in chronic renal failure progression and its unfavorable consequences. Various factors including oxidative stress, metabolic acidosis, decreased clearance of pro-inflammatory cytokines, obesity, infections and dialysis access problems contribute to micro-inflammation in chronic renal failure or hemodialysis. Recently much attention has been directed toward, the possible association between the alterations in gut microbiota composition and intestinal barrier which detected to aggravate inflammation and oxidative stress in chronic renal failure patients. There are some factors that can potentially affect gut microbiota composition such as exercise, smoking, and diet including macronutrient, polyphenol, fiber, and vitamins. Thus, altering life-style with a healthy diet and regular physical activity are important to prevent inflammation disease. However, more high quality study involving randomized controlled trials seems necessary in this field.

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Introduction

Kidney fibrosis is the main characteristic of chronic renal failure progression and classically is the result of chronic inflammation. Likewise chronic renal failure results to a systemic inflammation and oxidative stress which play a key role in chronic renal failure progression and its unfavorable consequences (1). Various factors including oxidative stress, metabolic acidosis, decreased clearance of pro-inflammatory cytokines, obesity, infections and dialysis access problems contribute to micro-inflammation in chronic renal failure or hemodialysis. In fact, irrespective of having clinical manifestations or different etiologies, most chronic fibrotic abnormalities have in common a persistent creation of angiogenesis factors, fibrogenic cytokines, reactive oxygen species, growth factors and also proteolytic enzymes. These

*Corresponding author: Professor Azar Baradaran,
Email: azarbaradaran@med.mui.ac.ir

situations stimulate deposition of extracellular matrix which progressively damages the renal architecture and accordingly its function (2).

Materials and Methods

For this review, we used a variety of sources by searching through PubMed, EMBASE, Scopus and directory of open access journals (DOAJ). The search was performed by using combinations of the following key words and or their equivalents; chronic renal failure, hemodialysis, tight junction, oxidative stress and gut microbiota.

Oxidative stress in chronic renal failure

Recent investigation, have detected that, reactive oxygen species, have been associated with renal fibrosis in various diseases including diabetic kidney disease or chronic transplant nephropathy following renal transplantation. Additionally, reactive oxygen species have been detected as the crucial mediators of the unfavorable effects of the renin-angiotensin-aldosterone system in kidney and vascular bed. Renal fibrosis in diabetes, aging and ischemia/reperfusion damage has been associated to extreme production of reactive oxygen species that is considered the main pathogenic pathway in these diseases (3). Oxidative stress extends from an imbalance between antioxidant defense mechanisms and reactive oxygen/nitrogen species creation that can cause tissue and vascular injuries and also nucleic acid damage in chronic kidney failure patients. The enhanced production of reactive oxygen/nitrogen species, bothered non-enzymatic or enzymatic antioxidant protection mechanisms, and other risk factors containing hyperhomocysteinemia, hemodialysis-associated membrane bio-incompatibility, deficiency of arylesterase/paraoxonase, uremic toxins (indoxyl sulfate), gene polymorphisms and endotoxin in individuals with chronic renal insufficiency can stop normal cell function by damaging cell proteins, amino acids, arachidonic acid derivatives ,lipids, carbohydrates and nucleic acids. The reactive oxygen species excess is linked to modifications in mitochondrial metabolism leading to cell damage. Reactive oxygen species are found as the normal products of the aerobic metabolism. They are consist of, for example, hydrogen peroxide (H_2O_2), peroxynitrite ($ONOO^-$), hydroxyl radical (-OH) superoxide and anion (O_2^-). Mitochondria are the primary source of reactive oxygen species, and it is well detected that alterations in mitochondrial function may result to overproduction of superoxide. Various conditions which affect kidney intensifies glomerulosclerosis and also interstitial fibrosis. These conditions act at cellular level by increasing the number of mutations in nuclear and mitochondrial DNA, advanced glycation end products, lipofuscin, increased oxidative stress and consequent increased apoptosis. For example in ischemia/reperfusion damage in the kidney creates excess of reactive oxygen species, making cell injury. Indeed, oxidative stress and inflammation act toward to overproduction of reactive oxygen species, which leads to kidney tissue fibrosis and progressive chronic disease. Importantly oxidative stress induces the production of inflammatory cytokines that will, lastly, induce free radical production and other various mediators and markers of cellular dysfunction, which lead to overproduction of glomerulosclerosis, extracellular matrix, apoptotic cells and up-regulation of pro-inflammatory genes may be linked to the superoxide excess and exhibit an accelerated renal failure process with resultant function loss (4). In uremia, increased concentration of malondialdehyde produced by lipid peroxidase and decreased function of antioxidant systems because of low levels of superoxide dismutase and glutathione (GSH) peroxidase have been detected, which leads to high cardiovascular mortality and morbidity, cachexia, anemia and a high risk for developing malignancy in these patients. In uremic patients, plasma concentration of chemokines and pro-inflammatory cytokines is constantly raised and circulating leukocytes are found to be activated and they produce reactive oxygen species in end-stage kidney failure patients (5). It should remember that, inflammation and oxidative stress are inseparably connected as each causes and aggravates the other. By activating the transcription factor, nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) as the master regulator of pro-inflammatory cytokines and chemokines, and by promoting formation of oxidized lipoproteins and glycoxidation products, oxidative stress triggers inflammation. Conversely inflammation triggers oxidative stress by triggering making of reactive oxygen, nitrogen and halogen species through the activated immune cells (6). Systemic inflammation in chronic renal failure and end-stage renal failure individuals commonly leads to the reduction of serum total cholesterol, low-density lipoprotein-cholesterol, albumin, high-density lipoprotein-cholesterol and also transferrin saturation and conversely leads to elevation of serum triglycerides and ferritin blood concentrations. The main clinical features and consequences of inflammation in chronic renal failure patients include frailty, disturbed physical strength, inducing erythropoietin-resistant anemia and also, increased risk of cardiovascular events, hospitalization and finally death (7).

Relationship of kidney and the gastrointestinal tract in renal failure

Recently much attention has been directed toward, the possible association between the alterations in gut microbiota composition and intestinal barrier which detected to aggravate inflammation and oxidative stress in chronic renal failure patients (6). In fact, integrity of the gastrointestinal epithelial cell tight junction that, seals the gap of the epithelial cells is essential to prevent the entrance of antigens, microbial toxins and other harmful luminal contents into the submucosal area and eventually in the body's internal environment. The main function of the intestinal mucosa are absorption of nutrients, working as a barrier to inhibit absorption of waste products and importantly the entry of luminal microorganisms and

their harmful by-products in the host's internal tissue and also secretion of waste products (8). By enabling the influx of these products into the internal environment, injury of the intestinal epithelial barrier function and structure results to local and systemic inflammation. The human gut contains more than 100 trillion microbial cells that affect metabolism, physiology, nutrition and immune function of the host. For remembering, the intestinal epithelial barrier includes of the apical plasma membrane of the enterocytes that regulates active and passive transcellular transport of solutes regularly through its specific transport channels and the apical junctional complex that makes the barrier against para-cellular permeation of luminal materials (9). Under normal situation, the intestinal epithelial tight junction stops para-cellular penetration of bacteria and their toxic by-products, degraded food material and also digestive enzymes. The apical junctional complex consists tight junction and the subjacent adherent's junction that firms the tight junctions. There is growing data supporting the presence of gastrointestinal barrier dysfunction and its role in the provocation of systemic inflammation in renal failure subjects (10). Various investigations had shown, intestinal permeability to large molecular weight polyethylene glycols is intensified in in renal failure. Additionally in uremia, luminal bacteria penetrate the intestinal wall and lodge in the mesenteric lymph nodes. Likewise in hemodialysis individuals commonly exhibit histological findings of chronic inflammation through the gastrointestinal tract and importantly endo-toxemia is consistently exist in dialysis patients in the absence of clinical infection. These findings point to strengthened intestinal permeability and barrier dysfunction in individuals with chronic renal failure (5). The mechanism by which renal failure increases intestinal epithelial permeability was not fully understood. In some situations, like in Crohn's disease, heat stroke, alcoholic hepatitis, ulcerative colitis and *Escherichia coli*, *Clostridium difficile* and *Vibrio cholera* infections, the intestinal tight junction barrier is disturbed permitting permeation of luminal antigens and pro-inflammatory substances into the underlying intestinal tissue. This results to activation of dendritic cells and T lymphocytes, release of pro-inflammatory cytokines, and the resident macrophages, and also recruitment of circulating inflammatory cells. Hence, local production and release of mentioned cytokines, finally, cause further interruption of the tight junction barrier by promoting endocytosis and degradation of claudin-1 and occludin proteins, as the key tightening transcellular components of the tight junction system. Therefore, injury of tight junction furthers the inflammation and inflammation by itself disturbs tight junction, initiating a self-perpetuating vicious cycle in these circumstances (7). Anatomic point of view, showed that gastrointestinal system is at the interphase between the blood and the potentially toxic substances of the intestine. Morphologic alterations, consisting of elongation of the crypts, diminution of villous height, and infiltration of lamina propria by inflammatory cells are noted in chronic renal failure. Moreover chronic renal failure increases intestinal permeability too. Furthermore, the interruption of colonic epithelial tight junction may subsequently result to translocation of bacteria and endotoxin along the intestinal wall. Studies showed, the tight junction barrier consists of the transmembrane, cytosolic, and peri-junctional proteins. In renal failure depletion of the key tight junction protein constituents in colon was seen. Various substances like urea and the byproducts of its hydrolysis through microbial urease are the main mediator of uremia-induced disruption of the intestinal barrier function and structure. Thus ammonia and ammonium hydroxide, as the byproducts of urea hydrolysis, further aggravates this condition and could impose a of local inflammation not only in the colon but also through all parts of the gastrointestinal system (4). This evidence imply that the disturbance of the epithelial barrier function and structure may occur in other segments of the gastrointestinal tract too. Studies regarding hemodialysis-provoked systemic circulatory stress and recurrent regional ischemia may also cause an injury to the mechanical barrier of the gut too. Additionally, conditions which promote intestinal dysbiosis may also attribute to the leaky gut in dialysis patients. Consequently, gut microbiome dysbiosis is related to bacterial translocation, hence, attributing to micro-inflammation in dialysis and also in patients with end-stage renal failure not yet on dialysis. Therefore, it is reasonable to modify the biochemical ambiance of the intestine, while uremia significantly alters the composition of microbiome, a condition that may attribute to the prevailing inflammation and uremic toxicity through disrupting the symbiotic association and formation of potentially harmful byproducts. Various factors of the lifestyle change the gut microbiota including diet and exercise (11).

Exercise

Some evidence indicates that exercise may alter the gut microbiota so exercise may be another main factor in the relationship between the microbiota, host metabolism, and host immunity. Animal and human study shows microbiota diversity rates positively correlated with plasma creatinine kinase quantities which is a marker of extreme exercise and protein intake, so it suggested that both diet and exercise change microbial diversity. However, extremities of exercise are frequently associated with dietary extremes, Thus the effect and mechanism underlying the single effects of exercise on microbiota is still unknown (12).

Smoking

Recent study shows cigarette smoking has an impression on gut microbiota. This influence might partially explain weight gain, which is seen after smoking cessation. Indeed, there is the modification in the gut microorganisms, which leading to more effective extraction of calories

from ingested food. These new discoveries create new fields of diagnostic and therapeutic methods via the control of the microbiota (13).

Diet

Study revealed short or long-term dietary habit is one of the most important factors that influence the composition and diversity of the human intestinal microbiota. The dietary affect on microbial metabolism throughout some paths include rising intestinal permeability, modifying the nutrients bacterial fermentation, disturbances intestinal function by activating both innate- and adaptive-immune responses. Both macronutrients and micronutrients form the gut microbial environment (14).

Macronutrients

Carbohydrate fermentation produces diverse metabolites that are main determinant of microbial composition such as short-chain fatty acids (SCFA) including butyrate, acetate, and propionate that can affect on gut microbiota. Protein fermentation causing the production of SCFA, ammonia, phenylacetate, phenylpropionate, indole acetate and propionate that some of them are potentially toxic and all of them change gut microbiota. In addition, quantity and quality of dietary fat modifies intestinal microbiota composition by its effect on bile acid composition and secretion (15).

Type of fat

The studies in animal shows that saturated fatty acids (SFAs) and polyunsaturated fatty acids (PUFAs) have different effects on gut microbiota. The SFA-rich diet caused significantly more reductions in Bacteroidetes-to-Firmicutes ratio than did the PUFA-rich diets. In vitro studies, differential impressions of SFAs and PUFAs on gut bacterial profiles were seen that cause selective antibacterial effect by different fatty acid. Some mechanisms have been offered for the antibacterial influences of free fatty acids, comprising: integration into membranes, production of reactive oxygen degradation derivatives, and intervention with enzyme function. Human study about the effect of type of fat on gut microbiota is rare but in a study has been revealed that fish oil with a high amount of n-3 PUFAs can change the gut microbiota (16).

Dietary fiber

Dietary fibers are food components that are indigestible for human enzymes and supply substrates for the gut microbial metabolism. Dietary fibers with different chemical components motivate the activity and growth of producing butyrate bacteria and lactobacilli and Bifidobacteria, and decrease Firmicutes-to- Bacteroidetes ratio so produce special component that have anti-inflammatory activities (17).

Polyphenols

Polyphenols are phytochemicals present in fruits, vegetables, and other products such as chocolate, coffee, tea, and wine. There are a two-way interaction between phenolic and microbiota. The dietary polyphenols and their metabolites have the ability to modulate the gut microbial balance via the motivation the growth of beneficial bacteria, while competitively exclude pathogen bacteria and applying prebiotic-like properties. Otherwise, the gut microbiota modifies the bioavailability, production and, consequently, the biological actions of phenolic metabolites. However, information about the impression of polyphenols on the gut microbiota and their action mechanisms in human are rare (18).

Vitamin D

There is developing evidence that the vitamin D pathway might be important in gut homeostasis and in relationship between the microbiota and the host. As regard the role of vitamin D in development and function of Treg and dendritic cell, the vitamin D status probably modify the impression of the intestinal microbiota on the immune system. Furthermore, recent investigation revealed the vitamin D receptor (VDR) directly suppresses the bacteria-induced nuclear factor-kB activation also homing of T cells to the gut decreased in the absence of VDR, on the otherwise the distribution and expression of VDR in intestinal epithelial cells influenced by commensal bacterial colonization, thus it shows a dynamic relationship between these bacteria and the receptor. Finally, vitamin D supplementation in deficient person might be a way to improve the composition of the bacterial microbiome and inflammation diseases (19).

Probiotics

Probiotics are live organism, which have benefit to the host when provided in adequate amounts. Probiotics such as Lactobacilli, Bifidobacteria species, and Streptococci modify the gut immune response and return intestinal homeostasis. Probiotics are naturally present in foods and supplements (20).

Prebiotics

Prebiotics are non-digestible food ingredient that causes certain changes, both in the composition and/or activity of the gut microbiota. Inulin and oligo-fructose that are natural food ingredients or dietary fibers, present in particular plants as storage carbohydrates, are two dietary nondigestible oligosaccharides, which have all the criteria for prebiotic classification. Therefore, these nutrients restore a healthy gut microbiota and they are being explained as new therapeutic methods to cure inflammatory illnesses (21).

Conclusion

Inflammation is a continuous aspect and is a main mediator of the progression of chronic renal failure and its several complications, such as cardiovascular complications. Renal failure results in disintegration of the colonic tight junction system, a phenomenon, which can attribute to

the systemic inflammation and account for the previously established evidence of defective intestinal barrier function in uremic subjects. There are some factors can affect on gut microbiota composition such as exercise, smoking, and diet including macronutrient, polyphenol, fiber, vitamins. Thus, altering life-style with a healthy diet and regular physical activity are important to prevent inflammation disease. However, more high quality study involving randomized controlled trials seems necessary in this field.

Authors' contribution

AB, HN, PN and MRK conducted literature review and wrote the article. MK completed the paper. SA finalized the paper. All authors read and signed the manuscript.

Conflicts of interest

The authors declared no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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References

1. Ramezani A, Raj DS. The gut microbiome, kidney disease, and targeted interventions. J Am Soc Nephrol. 2014;25(4):657-70.
2. Vaziri ND, Yuan J, Rahimi A, Ni Z, Said H, Subramanian VS. Disintegration of colonic epithelial tight junction in uremia: a likely cause of CKD-associated inflammation. Nephrol Dial Transplant. 2012;27(7):2686-93.
3. Fujii H, Nakai K, Fukagawa M. Role of oxidative stress and indoxyl sulfate in progression of cardiovascular disease in chronic kidney disease. Ther Apher Dial. 2011;15(2):125-8.
4. Vitetta L, Linnane AW, Gobe GC. From the gastrointestinal tract (GIT) to the kidneys: live bacterial cultures (probiotics) mediating reductions of uremic toxin levels via free radical signaling. Toxins. 2013;5(11):2042-57.
5. Mafra D, Lobo JC, Barros AF, Koppe L, Vaziri ND, Fouque D. Role of altered intestinal microbiota in systemic inflammation and cardiovascular disease in chronic kidney disease. Future Microbiol. 2014;9(3):399-410.
6. Vaziri ND, Zhao YY, Pahl MV. Altered intestinal microbial flora and impaired epithelial barrier structure and function in CKD: the nature, mechanisms, consequences and potential treatment. Nephrol Dial Transplant. 2015. pii: gfv095.
7. Mafra D, Fouque D. Gut microbiota and inflammation in chronic kidney disease patients. Clin Kidney J. 2015;8(3):332-4.
8. Sung CC, Hsu YC, Chen CC, Lin YF, Wu CC. Oxidative stress and nucleic acid oxidation in patients with chronic kidney disease. Oxid Med Cell Longev. 2013;2013:301982.
9. Vaziri ND. Gut microbial translocation in the pathogenesis of systemic inflammation in patients with end-stage renal disease. Dig Dis Sci. 2014;59(9):2020-2.
10. Pedersen G. Development, validation and implementation of an in vitro model for the study of metabolic and immune function in normal and inflamed human colonic epithelium. Dan Med J. 2015;62(1):B4973-B.
11. Viladomiu M, Hontecillas R, Yuan L, Lu P, Bassaganya-Riera J. Nutritional protective mechanisms against gut inflammation. J Nutr Biochem. 2013;24(6):929-39.
12. Hold GL. The gut microbiota, dietary extremes and exercise. Gut. 2014;63(12):1838-9.
13. Begon J, Juillerat P, Cornuz J, Clair C. Smoking and digestive tract: a complex relationship. Part 2: Intestinal microblota and cigarette smoking. Rev Med Suisse. 2015;11(478):1304-6.
14. Kovatcheva-Datchary P, Arora T. Nutrition, the gut microbiome and the metabolic syndrome. Best Pract Res Clin Gastroenterol. 2013;27(1):59-72.
15. Liu WY, Lu da J, Du XM, Sun JQ, Ge J, Wang RW, et al. Effect of aerobic exercise and low carbohydrate diet on pre-diabetic non-alcoholic fatty liver disease in postmenopausal women and middle aged men--the role of gut microbiota composition: study protocol for the AELC randomized controlled trial. BMC Public Health. 2014;14:48.
16. Yu HN, Zhu J, Pan WS, Shen SR, Shan WG, Das UN. Effects of fish oil with a high content of n-3 polyunsaturated fatty acids on mouse gut microbiota. Arch Med Res. 2014;45(3):195-202.
17. Rose DJ. Impact of whole grains on the gut microbiota: the next frontier for oats? Br J Nutr. 2014;112 Suppl 2:S44-9.
18. Cardona F, Andres-Lacueva C, Tulipani S, Tinahones FJ, Queipo-Ortuno MI. Benefits of polyphenols on gut microbiota and implications in human health. J Nutr Biochem. 2013;24(8):1415-22.
19. Ooi JH, Li Y, Rogers CJ, Cantorna MT. Vitamin D regulates the gut microbiome and protects mice from dextran sodium sulfate-induced colitis. J Nutr. 2013;143(10):1679-86.
20. Rajkumar H, Mahmood N, Kumar M, Varikuti SR, Challa HR, Myakala SP. Effect of probiotic (VSL#3) and omega-3 on lipid profile, insulin sensitivity, inflammatory markers, and gut colonization in overweight adults: a randomized, controlled trial. Mediators Inflamm. 2014;2014:348959.
21. Ceapa C, Wopereis H, Rezaiki L, Kleerebezem M, Knol J, Oozeer R. Influence of fermented milk products, prebiotics and probiotics on microbiota composition and health. Best Pract Res Clin Gastroenterol. 2013;27(1):139-55.

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