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New Tricks for Old Friends: Treating Gut Microbiota of Patients With CKD

RECENT OMICS-BASED STUDIES have helped elucidate the influence of gut microbiota on human health and disease. The diverse community of microorganisms that inhabit the human intestine has essential roles in host immunity and producing numerous bioactive metabolites that influence the host metabolism. Interesting, chronic metabolic disorders, despite their specifics, shared abnormalities in the composition and function of the intestinal microbiota, which can be associated with a low-grade chronic inflammation that is characteristic of disease phenotypes.[1]

Regarding chronic kidney disease (CKD), there is a bidirectional cause-effect relationship with gut microbiota.[2] In patients with CKD, the accumulation of uremic metabolites leads to changes in the composition and functionality of the gut microbiota and intestinal barrier disruption.[3] On the other hand, the presence of dysbiosis in these patients leads to increased production of substances resulting from gut microbial metabolisms, such as uremic toxins, including indoxyl sulfate, *p*-cresyl sulfate, *N*-trimethylamine *N*-oxide (TMAO), and indole acetic acid, which are associated with inflammation and oxidative stress.[3,4] These disorders in the gut microbiota, associated with the accumulation of toxins in the blood, aggravate several complications in patients with CKD by activating the immune system and leading to changes in other organs. Thus, gut microbiota may be seen as the cross-road between CKD and the phenotype of inflammation and oxidative stress that is typical in CKD.[4]

There is a growing interest in therapeutic strategies to modulate the gut microbiota in patients with chronic diseases. Several studies investigate the influence of nutrients, bioactive compounds from botanical foods, prebiotics, probiotics, symbiotics, postbiotics, and also physical exercise in microbial composition and functions.[1,3,5]

Diet is the main factor responsible for variations in the gut microbiome, and change can be fast.[6,7] Indeed, David et al.[8] observed that after 5 days with different diets (vegetarian and animal protein), the gut microbiota composition was altered in healthy individuals, and the animal protein-based diet provoked an increase in the abundance of the genera *Alistipes*, *Bilophila*, and *Bacteroides*, and a reduction in the genera *Roseburia*, *Eubacterium rectale*, and *Ruminococcus bromii*, which can metabolize polysaccharides. Therefore, the "food as medicine" approach in culinary medicine can be considered a strategy to target gut microbiota in CKD.[5,9] A high-intake animal protein-based diet and a low intake of dietary fiber change the gut microbiota, increasing the bacteria *Hungatella*, a trimethylamine (TMA) producer that leads to the high TMAO levels, which is a uremic toxin associated with inflammation and cardiovascular disease.[10]

Food is considered the primary driver of the gut microbiota composition; thus, more attention should be paid to patients with CKD regarding nutrition modulation of microbiota be leverage for disease management.[11-14] Researchers are evaluating the potential therapeutic strategies to modulate the gut microbiota in these patients. In fact, recent studies have shown that probiotics, prebiotics, and symbiotics can be effective on that modulation.[3] A recent systematic review and meta-analysis of randomized controlled trials concluded that prebiotic, probiotic, and symbiotic have a beneficial effect on metabolic, inflammatory, and oxidative stress markers. However, more studies are needed to evaluate the changes in gut microbial composition promoted by food interaction in patients with CKD.[15]

The assessment of responses to therapeutic interventions on the gut microbiota profile is arduous due to the complexity of this ecosystem and various factors that can impact this response.[16-21] Probiotics were the first strategies Hida et al.[22] used to modulate the gut microbiota in CKD, but the benefits remained controversial. Prebiotics and symbiotics are also studied as potential beneficial strategies for patients with CKD.[17,23,24]

In a pilot study published in this issue of the *Journal of Renal Nutrition* on the relationship between consumption of the prebiotic fiber inulin and gut microbiota composition and its metabolites, Biruete et al.[25] showed that inulin consumption for 4 weeks increased the relative abundance of the phylum Verrucomicrobia. However, they did not observe any change in the other parameters evaluated. This paper was very well controlled and designed with fascinating data, which additionally showed the impact of

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the drug sevelamer, body mass index, and gender on the gut microbiota composition of CKD patients, opening the way to new and more extensive studies. Nevertheless, the study should be qualified for certain limitations like the sample size, the accurate adherence of the supplementation, and the "low" amount of the inulin supplementation (10 and 15 g). Another paper published in the Journal regarding gut microbiota by Yang et al.[26] is a meta-analysis that observed the effects of dietary fiber intake on uremic toxins produced by the gut microbiota. Despite the small number and heterogeneity between studies evaluated (10 randomized controlled clinical trials involving 292 patients with CKD), the authors concluded that dietary fiber supplementation could reduce uremic toxin levels, with more evident effects in patients on dialysis and without diabetes. However, more studies should be addressed to establish the amount and type of fibers to promote the beneficial effects.

In addition to the prebiotics, several hypotheses have been addressed on this topic focusing on bioactive compounds from food that may be effective strategies for gut microbiota modulation as well as mitigation of inflammation and oxidative stress in patients with CKD.[3,27,28] Polyphenol-rich foods like grape, red wine, pomegranate, garlic, green tea, chocolate, propolis, turmeric, blueberry, and cranberry may modify the gut microbiota composition due to their bacteriostatic or bactericidal actions.[5,27-31] On the other hand, the enzymatic activity of the gut microbiota contributes to the breakdown of the oligomeric and polymeric polyphenol structures into the low molecular weight phenolic metabolites, increasing their bioavailability.

It is crucial to notice that diet can provoke both malefic and salutary effects on the gut microbiota, for example, high red meat and eggs consumption may increase the production of toxins as TMAO, indoxyl sulfate, and *p*-cresyl sulfate due to fermentation of some amino acids, carnitine, and choline by the gut microbiota.[32,33] Also, studies suggest that both higher dietary intake of salt and sugar may deleteriously alter the gut microbiota composition.[34,35] Alcohol has been associated with modification in gut microbiota, leading to increased Proteobacteria and Actinobacteria phyla and a decrease of Firmicutes.[36] Artificial sweeteners may increase Firmicutes and alter gut microbiota in mice,[37] and micronutrients supplementation (e.g., oral iron) can result in a remarkable change in the microbiota.[38] Gut microbiota can also be affected by environmental chemicals (pesticides, herbicides, insecticides), which have been increased exponentially in the contemporary era.[39]

In contrast, beneficial strategies have shown to effectively decrease uremic toxins in patients with CKD, such as a low protein diet in which the red meat intake is low.[40] Taken together, a low protein diet is associated with lower phosphorus intake, which is well-known to bring beneficial effects to these patients. However, little is known about its effects on gut microbiota. In another study published in this issue of the Journal, Zhang et al.[41] showed the difference between a standard and low phosphorus diet in a selected group of healthy men. After 5 days of intervention for each type of diet, they observed a shift in the intestinal microbiome in the low phosphorus diet group, where an increase in the relative abundance of beneficial microbes was noted, in addition to other interesting results in biochemical analysis. However, these changes, mainly the intestinal microbiome, were attributed to phosphorus diet content since the carbohydrate and protein diet content was changed in the low phosphorus diet. Thus, these findings are promising contributions to other studies in this area.

The influence of diet on gut microbiota composition is very complex. However, food intake is the primary factor that influences the gut microbiota composition and diversity, and evaluation of different kinds of foods on the gut microbiota in CKD patients should take new aspects into account. The articles discussed in this commentary highlight the importance of diet to the gut microbiota metabolism in patients with CKD; hence, renal dietitians should pay attention to all diet prescriptions, not only for kidney function and complications in these patients but also to treat well the microorganism living in their body. Altogether the effects of food intake on the microbiota in CKD patients deserve further studies.

This issue of the Journal also addresses some issues associated with the importance of metabolic balance in patients with kidney disease. Hypertension associated with elevated homocysteine levels, known as H-type hypertension, may place patients at greater risk for CKD and cardiovascular events. In a registry study of H-type hypertension, Shi et al.[42] examined these associations while adjusting for age, body mass index, waist circumference, smoking, drinking, blood pressure, lipid profile, and medication use in a cohort of 12,873 patients. They found that people with H-type hypertension having homocysteine levels >22 μmol/L had increased risk for CKD and lower kidney function in the multivariate analyses. Although following a cohort of 746 patients with CKD for almost 5 years, Galán et al.[43] demonstrated hypermagnesemia to be associated with cardiovascular events and all-cause mortality in patients with CKD. The findings held across univariate, multivariate, and propensity score analyses. Their results suggest caution when using magnesium supplementation in CKD. In a report by Haghighatdoost et al.,[44] it was demonstrated that the net endogenous acid production was associated with calcium oxalate stone production in patients with CKD, independent of dietary potassium and protein intake. Metabolic rate was assessed by Vilar et al.[45] using the gold-standard doubly labeled water technique for total energy expenditure and indirect calorimetry for resting energy expenditure. They assessed whether levels of kidney function in 80 patients at differing stages of CKD were associated with changes in metabolic rate. Their study demonstrated no differences in energy metabolism between patients with eGFR <50 and ≥ 50 mL/min/1.73 m^2 after adjusting for age, sex, and weight.

Other contributions in this issue of the *Journal of Renal Nutrition* address concerns related to helping patients with CKD make changes in their diet and lifestyle. Implementation of behavioral modification in patients with CKD was examined by Okubo et al.[46] who reports on the cost-effectiveness of implementing behavior modification as evaluated in the Frontier of Renal Outcome Modifications in Japan (FROM-J) study. They determined that the behavior modification delivered by dietitians together with practice guidelines implementing the program in primary care settings was cost effective as demonstrated by fewer canceled visits, more nephrology referrals, and slower progressive decrease in kidney function. Adherence to pharmacotherapy and life style recommendations for patients having maintenance hemodialysis or kidney transplant was evaluated by Nowicka et al.[47] using a self-assessment questionnaire. They determined that kidney transplant recipients rated their knowledge higher and reported a higher adherence rate than the patients on hemodialysis. Assessing physical performance of patients requiring maintenance hemodialysis using the Health-related Quality of Life questionnaire was examined by Matsuzawa et al.[48] They demonstrated that the 10 items in the questionnaire associated with physical functioning were associated with measured physical performance and could be used as a surrogate for formal physical function assessment. Telehealth for medical nutrition therapy[49] continues to be an important option for delivery of medical nutrition therapy for patients with CKD. In this issue of the Journal, telehealth is addressed by a personal perspective from Betz[50] who routinely provides virtual MNT, especially during the recent Coronavirus Disease 2019 (COVID 19). She outlines some advantages and disadvantages observed during the process of managing nutrition care for nephrology patients, including increased scheduling and show rates. The Patient Education[51] offering in this issue of the Journal also addresses telehealth and provides a handout to be used for patients that explains the terms and definitions of telehealth.

In the United States, discussions surrounding staffing ratios in dialysis centers continue. Currently, eight states in the United States have staffing ratio requirements for dialysis facilities but only one state (Texas) has ratio requirements for dietitians.[52] Hand et al.[53] continue a series of investigations into patient:dietitian staffing ratios in dialysis facilities in the United States. In the latest report, comparisons are made between the mandated patient:dietitian ratio required by the State of Texas of $<$125:1 to comparable facilities elsewhere in the United States that do not require a staffing ratio. Significant differences were noted between Texas and other regions for patient:dietitian staffing ratios. More areas outside of Texas had ratios $>$125:1 but, even within Texas, the number of facilities having $>$125 patients is fewer, indicating that more dialysis facilities are smaller in current times compared to when the Texas mandate was first enacted (ca. 1999). Unfortunately, the Centers for Medicare and Medicaid Dialysis Facilities Report does not allow for a deeper examination into the quality of professional practice such as that noted by McClellan[54] who reported that standardized mortality ratios were impacted by, among other factors, dietitian practice pattern (one of 5 factors explaining 31% of mortality rates). We hope these important issues continue to be examined by this team and others.

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