CLINICAL BRIEF

The Kidney–Gut Axis: Implications for Nutrition Care

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There is increasing clinical evidence that patients with chronic kidney disease (CKD) have a distinctly dysbiotic intestinal bacterial community, termed the gut microbiota, which in turn drives a cascade of metabolic abnormalities, including uremic toxin production, inflammation, and immunosuppression, that ultimately promotes progressive kidney failure and cardiovascular disease. As the gut microbiota is intimately influenced by diet, the discovery of the kidney–gut axis has created new therapeutic opportunities for nutritional intervention. This review discusses the metabolic pathways linking dysbiotic gut microbiota with adverse health outcomes in patients with CKD, as well as novel therapeutic strategies for targeting these pathways involving dietary protein, fiber, prebiotics, probiotics, and synbiotics. These emerging nutritional interventions may ultimately lead to a paradigm shift in the conventional focus of dietary management in CKD.

Introduction

IN THE PAST 5 years there have been significant scientific developments linking gut health and several chronic diseases,[1] including kidney disease.[2] Indeed, recent findings have implicated the community of bacteria that reside in the large bowel, termed the gut microbiota, as a key player in the heightened risks of kidney failure progression and cardiovascular disease observed in patients with chronic kidney disease (CKD).[3] The gut microbiota is not only highly dependent on diet, but its plasticity makes it an attractive therapeutic target for dietary manipulation.[4] Therefore, the emerging role of gut health in CKD, which has been coined the "kidney–gut axis," is of significant importance to the dietetic community. The aim of this article is to describe the link between diet, gut microbiota, and clinical outcomes in CKD patients and then outline novel dietary interventions in the area of gut health.

Diet and CKD: The Origins and Link to Gut Health

A person's risk for CKD is determined by both genetic and environmental factors.[5] The significant rise in the prevalence of kidney disease within a single generation suggests a dominant role of environment in promoting CKD. One of the largest environmental factors a person is exposed to is what they eat. However, until recently, our understanding of the role of diet as an environmental risk factor has been restricted to its effect on human metabolism, without due consideration of its effect on intestinal bacterial metabolism and ensuing consequences for human health. The recent discovery of the gut microbiota's metabolic potential, which contains 100 times the genetic material of mammalian cells,[6] has uncovered a new pathway in which the diet can impact on health and disease (illustrated in Fig. 1). The implications of this in CKD are significant, with a number of studies demonstrating a distinct dysbiotic gut microbiota in this population.[7,8] Moreover, dietary recommendations in CKD may indirectly contribute to this dysbiosis, particularly in patients prescribed oxalate- and potassium-restricted diets.[9]

Diet–Gut Interaction

Dietary constituents that are not absorbed in the small intestine are rapidly fermented by the colony of bacteria in the large intestine. The two main types of bacterial fermentation are saccharolytic (carbohydrate) and proteolytic (protein). Saccharolytic is a more favorable type of fermentation because of the beneficial metabolites that it forms, including short chain fatty acids butyrate, propionate, and acetate.[10] These short chain fatty acids are not only integral to the health of the colonic epithelium, but have a myriad of other benefits, including anti-inflammatory properties.[11] Proteolytic fermentation, on the other hand, is known to be the source of a number of potentially toxic metabolites, particularly the key nephrovascular uremic toxins, indoxyl sulfate and p-cresyl sulfate.[12] The relative amount of saccharolytic versus proteolytic fermentation that occurs in the colon is intimately regulated by dietary nutrient availability, particularly the ratio of carbohydrate to nitrogen (protein) and colonic transit time.[13]

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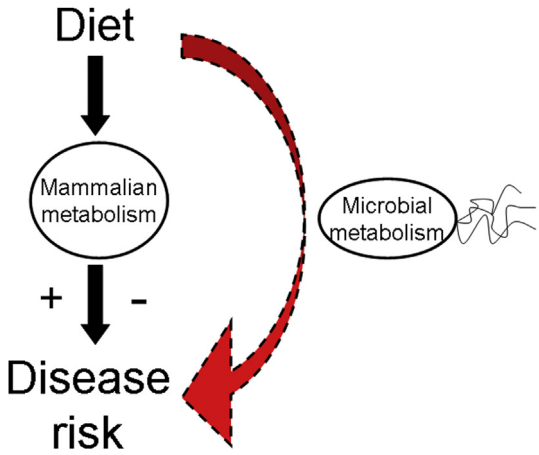

Figure 1. Two pathways in which diet can impact on disease.

Dietary Fiber

Dietary fiber is a broad term encompassing carbohydrates that are indigestible by human alimentary enzymes.[14] CODEX Alimentarius Commission recently adopted a comprehensive definition of dietary fiber, categorizing different types by their molecular weight and solubility (Fig. 2). There are a number of well-established benefits associated with dietary fiber, including reductions in total cholesterol and postprandial blood glucose levels.[15] Some of these benefits overlap between different types of dietary fiber, whereas others appear to be category specific. Nonetheless, there is currently insufficient evidence to suggest one type of fiber is superior to another and therefore the concept of "all fiber fits" to achieve the Dietary Reference Values is recommended.[16]

Dietary fiber may assume even greater importance in CKD patients based on additional benefits with respect to enhanced integrity of the gastrointestinal wall[17] (which has been shown to be "leaky" in CKD[18]) and reduced systemic levels of hazardous uremic toxins.[19] Furthermore, an analysis of 14,543 participants in the National Health and Nutrition Examination Survey III demonstrated that increases in dietary fiber intake were associated with statistically significant and clinically important reductions in inflammation and mortality in people with kidney disease and that these benefits were significantly more marked than those observed in patients without kidney disease.[20] Despite these findings, there is limited evidence from intervention studies, which have led to weak dietary fiber recommendations in renal nutrition guidelines.[9] There is, therefore, a clear need for further research investigating the role of dietary fiber in CKD. Additionally, there are a number of other aspects that dietitians need to consider when recommending dietary fiber in practice. These are summarized in Table 1.

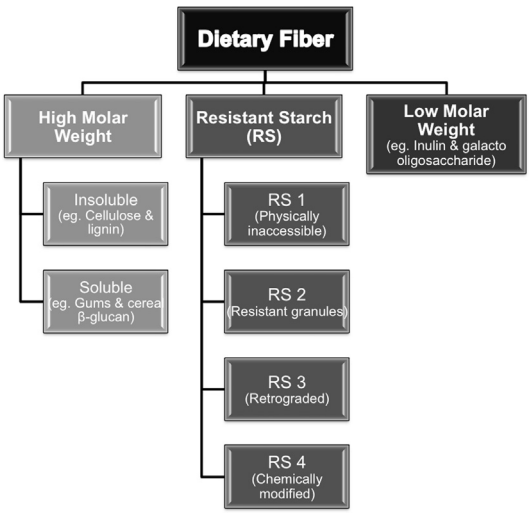

Figure 2. Dietary fiber categories.

Dietary Protein

There are a number of factors that impact on the availability of protein in the colon leading to increased proteolytic fermentation, including the efficiency of protein assimilation in the small intestine and colonic transit time. Protein assimilation in the small intestine is affected by protein load (amount), form (cooked or uncooked), and source (animal or plant),[21] as well as the presence of other dietary constituents (eg, resistant starch).[22] The impact of these variables can be significant, with studies in the healthy population demonstrating protein malabsorption of up to 35%.[23] In the CKD population, protein assimilation is known to be further impaired,[24] with a range of mechanisms thought to contribute, including acid suppression therapy,[25] gastroparesis, small-bowel bacterial overgrowth, and pancreatic abnormalities.[26]

Increased colonic transit time is another common symptom in patients with CKD, often secondary to patients' medical treatment.[27] Common factors likely to contribute include fluid restriction, medication load (including phosphate binders), and dietary restriction, particularly of higher fiber foods.

Targeting modifiable predictors of protein assimilation and delayed colonic transit time, in order to lower proteolytic fermentation, maybe a valuable, yet to date an underresearched strategy to improve gut health in CKD.

Targeting the Gut in CKD

The concept of using the gastrointestinal tract to treat kidney disease is not new in nephrology. The idea was first conceived by a Roman physician, Pedanius Dioscorides, over 2000 years ago as a means to eliminate toxin accumulation in kidney disease.[28] There have subsequently been a number of attempts to use the gut in CKD, including enteric intestinal dialysis,[29] yet the therapies' invasive nature coupled with limited knowledge, has inhibited translation in practice. It is only in recent years, with high throughput

Table 1. Points to Consider When Recommending Dietary Fiber in Practice

Points to Consider	Implications for Practice
Fiber content of food can be high variable based on different cooking and processing techniques (particularly in resistant starch)	Should we be encouraging specific cooking and cooling techniques?
Most countries' nutrient composition tables are out dated where dietary fiber estimates do not include important subcategories of resistant starch and low molecular weight oligosaccharides[43]	Are we under estimating the fiber benefits of some foods?
The latest Codex definition recognizes all substances that behave like fiber, regardless of how they are produced, should be considered as important sources of dietary fiber if they show physiological benefits	Fortification of food products with dietary fiber may be an important source for patients with chronic kidney disease who need to restrict some naturally occurring sources, such as in the case of hyperkalemia
Traditional "renal diets" are inherently lower in fiber based on potassium and oxalate restrictions	It is important to ensure patients are still receiving adequate dietary fiber when prescribing potassium- and oxalate-restricted diets

technologies providing a better understanding of the metabolic potential of the gut microbiota, that therapies targeting the gut are being revived in CKD.

There have been a number of drug therapies proposed to modify gut microbial metabolism, including alpha glucosidase inhibitors[30] and antibiotics,[31] however, diet-based interventions, given their typical innocuous nature, maybe a more attractive target.

Pre- and Probiotics in CKD

Prebiotics, the "indigestible" carbohydrates that stimulate bacteria, and probiotics, the live beneficial bacteria (such as *Bifidobacterium*), have been consumed as part of the diet of many cultures for thousands of years.[32] These naturally occurring components in health-promoting foods, described in Table 2, have more recently been cultivated by industry and are now widely available as commercial supplements and are in many fortified foods. A comprehensive product update on probiotics was recently provided by Zirker.[33]

Characterization of the dysbiotic gut microbiota in CKD provides a mechanistically sound rationale for the potential benefit of pre- and probiotics to re-establish microbial balance. There is a growing body of supportive evidence surrounding this therapy for targeting a wide range of common disturbances in CKD.[34] A summary of the potential benefits of pre- and/or probiotic supplementation, as well as their hypothesized mechanisms of action, is listed in Table 3. Extrapolation of findings from non-CKD clinical trials also suggest a number of other potential benefits for this therapy relevant in CKD such as blood glucose control,[35] hypertension,[36] weight management,[37] and urinary tract infections.[38]

Given the infancy of this area of research most of the proof-of-concept studies have relied on commercial supplements to provide precise and high dose quantities of pre- and probiotics. However, one of the fundamental principles of dietetic practice is to recommended nutrients from food sources as first line therapy, and it is only when this fails that supplements are used. This concept may also

Table 2. Naturally Occurring Sources of Pre- and Probiotics

Probiotic *"Live microorganisms which when administered in adequate amounts confer a health benefit on the host"*[44]		Prebiotics *"A selectively fermented ingredient that allows specific changes, both in the composition and/or activity in the gastrointestinal microflora that confers benefits upon host wellbeing and health"*[45]	
Food Source	Predominant Type*	Food Source	Predominant Type
Yogurts (fermented milk product)	Started cultures *Lactobacillus bulgaricus* and *Streptococcus thermophilus*[46]	Asparagus	Inulin[47]
Kefir (fermented milk beverage)	*Lactobacillus* and *Lactococcus* genera, and yeast[48]	Rye bread	Inulin[47]
Kombucha (tea)	*Gluconacetobacter*, *Lactobacillus* and *Zygosaccharomyces* (yeast)[49]	Canned beans	GOS[50]
Kimchi and Sauerkraut	*Leuconostoc*, *Lactobacillus*, *Pediococcus* and *Streptococcus genera*[51]	Lentils	GOS[50]
Natto (fermented soy beans)	*Bacillus subtilis* specie[52]	Nectarines	FOS[53]

FOS, fructo-oligosaccharides; GOS, galacto-oligosaccharide.

*The bacterial profile can differ depending on varieties, raw materials used, process, fermentation, and preservation methods.

Table 3. Target Treatment and Proposed Mechanisms of Pre- and/or Probioic Supplementation in Patients with Established Chronic Kidney Disease

Observed Benefit	Proposed Mechanisms
↓ Fecal vancomycin-resistant enterococci[54]	- Competitive colonization - Antimicrobial production ↓ Colonic pH
↑ Serum folate[55]	↑ Bacterial production of folate
↓ Serum uremic toxins	- ↑ Microbial metabolism
■ Urea[56]	- Competitive colonization
■ Uric acid[57]	- Antimicrobial production
■ Indoxyl sulfate[58]	- ↓ Colonic pH
■ p-Cresyl sulfate[59]	- ↓ Colonic transit time
■ Di-methylamine[60]	- ↓ Availability of substrate
↓ Serum phosphate[61]	↓Colonic pH ↑ the ionization of Ca which bind with intestinal phosphorus ions as an intrinsic binder
↓ Serum triglycerides[55]	↑ Bacterial production of nicotinic acid
↓ Serum homocysteine[55]	↑ Bacterial production of B vitamins
↑ Quality of life[62]	↓ Symptoms of uremia
↓ Urinary oxalate[63]	↑ Microbial metabolism of oxalate

translate to pre- and probiotics with support for the benefits of naturally occurring probiotics in animal models demonstrating foods such as kefir,[39] koumiss, and yoghurt[39,40] were able to improve renal injury. However, whether this translates *in vivo* is the source of ongoing debate with conflicting studies suggesting foods sources of probiotics are less effective when compared to commercial probiotic capsules based on their bile and acid resistance.[41,42]

Despite the growing interest and potential in CKD for pre- and probiotics (both commercial and natural sources), this area of research is in its infancy and further high quality clinical trials are needed before translation can occur.

Practical Application

There is evolving evidence implicating diet and its impact on colonic bacterial metabolism in the heightened risks of kidney failure progression and cardiovascular disease in CKD patients. This article presented a number of emerging concepts linking the diet and gut microbiota dysbiosis in CKD, with suggestions for how this may impact future clinical practice and ultimately lead to a paradigm shift in the focus of dietary advice in CKD, particularly with respect to fiber, protein, and pre-/probiotics.

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