REVIEW

Modulation of the Gut Microbiota by Resistant Starch as a Treatment of Chronic Kidney Diseases: Evidence of Efficacy and Mechanistic Insights

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ABSTRACT

Chronic kidney disease (CKD) has been associated with changes in gut microbial ecology, or "dysbiosis," which may contribute to disease progression. Recent studies have focused on dietary approaches to favorably alter the composition of the gut microbial communities as a treatment method in CKD. Resistant starch (RS), a prebiotic that promotes proliferation of gut bacteria such as *Bifidobacteria* and *Lactobacilli*, increases the production of metabolites including short-chain fatty acids, which confer a number of health-promoting benefits. However, there is a lack of mechanistic insight into how these metabolites can positively influence renal health. Emerging evidence shows that microbiota-derived metabolites can regulate the incretin axis and mitigate inflammation via expansion of regulatory T cells. Studies from animal models and patients with CKD show that RS supplementation attenuates the concentrations of uremic retention solutes, including indoxyl sulfate and p-cresyl sulfate. Here, we present the current state of knowledge linking the microbiome to CKD, we explore the efficacy of RS in animal models of CKD and in humans with the condition, and we discuss how RS supplementation could be a promising dietary approach for slowing CKD progression. *Adv Nutr* 2019;10:303–320.

Keywords: resistant starch, high-amylose maize starch, chronic kidney disease, diabetic nephropathy, microbiota, microbiome, short-chain fatty acids, uremic retention solutes

Introduction

Chronic kidney disease (CKD) affects ≤13% of the population worldwide (1); however, <1 in 10 affected individuals are aware they have the condition (2). Despite its underdiagnosis, the prevalence of CKD is increasing, particularly in low- and middle-income countries facing epidemic growths in obesity and diabetes and increased life expectancy. In the 2015 Global Burden of Disease Study, kidney disease was the 12th most common cause of mortality, accounting for 1.1 million deaths worldwide, and overall CKD mortality has increased by 31.7% over the last 10 y (3). In the United States, the treatment costs of CKD exceed $48 billion/y (4), placing a considerable burden on the health care system.

The 2 major clinical features seen in CKD are the progressive loss of kidney function over time and the development of cardiovascular disease (CVD). CKD is associated with a 2- to 3-fold increased risk of CVD mortality, and individuals with CKD are at higher risk of death from ischemic heart disease or stroke than they are of progressing to end-stage renal disease (ESRD) (5). Modifiable risk factors for CKD include overweight and obesity, diabetes, hypertension, and cigarette smoking (6); and preventative lifestyle intervention strategies to encourage healthy eating, physical activity, and smoking cessation are of vital importance. As kidney function declines, excess fluid, electrolytes, and nitrogen-based waste products accumulate in the circulation and contribute to the complications and end-organ damage associated with CKD. Current treatment methods for ESRD, such as dialysis, attempt to remove these wastes from the circulation. Many nitrogenous uremic toxins are of gut bacterial origin, and increasing evidence indicates that the

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Abbreviations used: AhR, aryl hydrocarbon receptor; CKD, chronic kidney disease; CVD, cardiovascular disease; ESRD, end-stage renal disease; GFR, glomerular filtration rate; GLP-1/2, glucagon-like peptide 1/2; HbA1c, glycated hemoglobin; IAA, indole acetic acid; IS, indoxyl sulfate; MCP-1, monocyte chemoattractant protein 1; PAG, phenylacetylglutamine; PCS, p-cresyl sulfate; ROS, reactive oxygen species; RS, resistant starch; T2D, type 2 diabetes; TMAO, trimethylamine-N-oxide; Treg, regulatory T cell.

intestinal microbiota is a potential therapeutic target for interventions to limit the effects of CKD.

Dysbiosis in CKD

Many diseases have been associated with alterations in the gut microbiota including liver disease (7), hypertension (8), obesity (9), and insulin resistance (10). It has recently been recognized that in patients with CKD there is a change in gut microbial ecology that may contribute to the pathogenesis of the disease (11). Early studies in hemodialysis patients showed lower viable counts of beneficial bacterial genera such as *Bifidobacteria*, and greater viable counts of *Clostridium perfringens* and aerobic bacteria including Enterobacteriaceae and *Enterococci* species compared with control subjects (12). When compared with healthy controls, patients with ESRD were found to have large increases in Actinobacteria, Firmicutes (especially the class Clostridia), and Proteobacteria (primarily Gammaproteobacteria) phyla (13). A follow-up study utilizing this same cohort identified that there were increases in bacterial families that possess uricase, urease, p-cresol–forming, and indole-forming enzymes (14) and hemodialysis patients have been shown to have higher fecal concentrations of indole and p-cresol than healthy controls (15). Several studies have identified that ESRD patients have a decrease in bacterial families possessing enzymes for the formation of SCFAs compared with healthy controls (14, 16). A recent pilot study comparing hemodialysis and peritoneal dialysis patients confirmed that ESRD patients have an altered microbiome compared with controls and also identified that the microbiome composition was different between modes of dialysis (17). These findings highlight that dysbiosis occurs during CKD and provide insights into the potential mechanisms that may be targeted through dietary interventions, which will be explored in greater detail below.

Prebiotics

Prebiotics are substrates that promote the growth of beneficial bacteria. The term "prebiotic" was first introduced in 1995 (18) and early attempts at defining prebiotics focused on those compounds that had beneficial effects on health-promoting groups of bacteria, namely *Lactobacilli* and *Bifidobacteria*, within the colon (19, 20). This definition of prebiotics led to 2 broadly characterized types of prebiotics: inulin-type fructans (inulin, oligofructose, and fructo-oligosaccharides) and galactans (galacto-oligosaccharides) (21). With regards to food labeling, these prebiotics are often classified as dietary fibers (22); however, there is no agreed-upon universal definition for the term "dietary fiber," which is sometimes used as an umbrella term that is inclusive of nonstarch polysaccharides and certain oligosaccharides (20). As the knowledge of the human gut microbiota increased it became apparent that there was more to healthy gut microbiota than just *Lactobacilli* and *Bifidobacteria*, and it was suggested that the definition of prebiotics be expanded to reflect this knowledge (23). A consensus statement has recently been published on the subject, defining a prebiotic as "a substrate that is selectively utilized by host microorganisms conferring a health benefit" (24) and expanding the list of substrates that may be considered prebiotics to include noncarbohydrate food components such as polyphenols, PUFAs, and conjugated linoleic acids.

Resistant Starch

Starch is a polymeric carbohydrate produced by most plants for the purpose of energy storage. Starch granules are composed of 2 polysaccharides: amylose, which is a linear molecule, and amylopectin, which is highly branched, making amylopectin easily accessible to digestive enzymes in the small intestine (25). Resistant starches (RSs) contain α-linked glucose molecules that are resistant to hydrolysis in the human small intestine, due to being either physically or chemically resistant to digestive α-amylases (26), and are categorized depending on the mechanism of enzymatic resistance. RS type 1 (RS1) is found in whole grains and legumes and is inaccessible to digestive enzymes because it is surrounded by a protective barrier. RS type 2 (RS2) products contain dense ungelatinized starch granules, such as high-amylose maize starch and raw potatoes. Retrograded starches, such as cooked and cooled potatoes, are categorized as RS type 3 (RS3). Retrogradation occurs when starches are first heated to undergo gelatinization and then cooled to form a crystalline structure. RS type 4 (RS4) is formed via chemical cross-linking of starch by the addition of esters and ether groups. These starches are often found in breads and cakes (27). Last, RS type 5 (RS5) forms when amylose and long branch chains of amylopectin form single-helical complexes with fatty acids and fatty alcohols, preventing enzymatic access to the starch (28). The different types of RS are outlined in **Table 1**. As RS passes into the large intestine it becomes available for fermentation by health-promoting colonic bacteria (28), which has led some commentators to refer to RS as a potential prebiotic (29). RS is a soluble, nonviscous fiber that is preferentially metabolized in the large intestine by saccharolytic bacteria (30) and consumption of RS represents a potential strategy for beneficially altering the human gut microbiome.

Metabolic effects of RS

Adequate dietary fiber consumption is associated with several health benefits, including reduced risk of obesity, metabolic syndrome, type 2 diabetes (T2D), CVD, colon cancer, and constipation (31–37). Soluble, highly viscous forms of dietary fiber such as β-glucan and psyllium are well known for their glucose- and cholesterol-lowering effects, as the gel-forming ability of these fibers slows gastric emptying and increases bile acid excretion (38). However, the association between RS consumption (a nonviscous, soluble fiber) and improvements in glucose and lipid metabolism is unclear. Human RS intervention studies performed to date have been of short duration, contained small sample sizes, and were of moderate to low methodological quality. Although some studies have found that RS supplementation is associated with reductions in total (39, 40) and LDL (39)

TABLE 1 Categories of RS[1]

RS type	Description	Examples
RS1	Physically inaccessible	Coarsely milled grains or seeds, legumes
RS2	Ungelatinized starch	Raw potato, unripe banana, high-amylose maize starch
RS3	Retrograded starch	Cooked, cooled foods (potatoes, pasta, rice), corn flakes
RS4	Chemically modified starch	Cross-linked starch and octenyl succinate starch
RS5	Amylose–lipid complex	Stearic acid–complexed high-amylose starch

[1] RS, resistant starch.

cholesterol, the majority of human clinical trials investigating the impact of RS on lipid concentrations have found no effects in healthy individuals, people who are overweight or obese, those with the metabolic syndrome, or subjects with T2D (41–49).

Digestible starch contributes 17 kJ/g to energy intake, whereas RS contributes ~8–10 kJ/g of metabolizable energy (50). Therefore, if RS replaces the same weight of digestible starch in a food product, it would be plausible to hypothesize that RS might assist with weight reduction. However, this does not appear to be the case in human trials, where participants have been observed to unconsciously compensate by increasing their kilojoule intake of other foods in order to remain weight-stable (51–53). Some researchers have found that RS consumption increases subjective satiety ratings (54, 55), although others have found no effect of RS on appetite and satiety ratings (51, 56, 57). A small number of animal studies have found that RS supplementation results in significant reductions in body weight, but the quantity of RS provided to rodents (≤500 g/kg diet) has far exceeded what is tolerable or realistic in humans (58–60). In summary, RS is unlikely to induce significant reductions in appetite or body weight.

RS and diabetes

Diabetes is a significant contributor to the development of CKD and it has been suggested that nondigestible carbohydrates, such as RS, may limit the progression of CKD via improvements in glycemic control (28). RS has been shown to attenuate postprandial glucose excursions in single-meal studies involving healthy-weight and obese subjects (61–63). Viscous soluble fibers lower postprandial glucose and insulin responses by dose-dependently increasing the viscosity of chyme in the stomach, slowing gastric emptying, and reducing the rate of carbohydrate digestion and absorption in the small intestine (64). However, RS is a nonviscous soluble fiber, so its contribution to postprandial glucose reductions is primarily due to the lower energy density of the RS in comparison to the digestible starch control. The majority of acute RS feeding studies performed to date have not provided the same quantities of available carbohydrate between treatment and control groups, so it has not been possible to determine whether postprandial glucose and insulin responses were reduced due to a unique property of the RS or simply due to the lower energy density and available carbohydrate in the test meals. In the small number of trials that have controlled for metabolizable energy by providing isoenergetic meals, RS supplementation significantly reduced postprandial blood glucose concentrations in healthy individuals and people with T2D (65–67). Further research is now needed in order to determine the mechanism whereby RS exerts its postmeal effects and the optimal RS type, dosage, and patient populations required to maximize glycemic improvements.

Whereas no reductions in fasting blood glucose concentrations have been observed in individuals consuming diets supplemented with RS (40, 42, 43, 45, 47, 48, 52, 68–71), improvements in insulin sensitivity have frequently been reported in trial participants who are overweight or obese, people with the metabolic syndrome, and those with T2D (53, 68–70, 72). However, studies using gold-standard techniques to assess insulin sensitivity (euglycemic-hyperinsulinemic clamp) have been unable to confirm these findings (52, 65). The effects of RS consumption on glycated hemoglobin (HbA1c) in individuals with T2D are contradictory. In a parallel randomized controlled trial, obese individuals with T2D consumed 24 g RS2/d for 4 wk (43). Although treatment resulted in significant reductions in body weight and improved insulin sensitivity compared with controls, there was no change in HbA1c, which could be partially due to the brief study duration. A longer (12-wk) trial providing 40 g RS2/d also failed to show any significant change in HbA1c in people with T2D (65). In contrast, 1 study undertaken in women with T2D who consumed only 10 g RS2/d for 8 wk reported a significant reduction in HbA1c (70, 73). Given the ability of RS to beneficially modify the composition of the gut bacteria and potentially improve some metabolic health abnormalities, it is interesting to consider whether RS may have beneficial applications in the management of CKD and the potential mechanisms for its action.

RS and CKD

An RS-supplemented diet has been shown to reduce plasma urea concentrations in both healthy animals (74, 75) and animal models of CKD (76); however, it should be noted that in the study by Younes et al. (76) the control group received a fiber-free diet. Compared with normal corn starch, supplementing the diet with 5%, 10%, or 20% RS did not ameliorate albuminuria in a streptozotocin-induced diabetes model (77). Supplementation with 20% RS did lead to reductions in urinary albumin concentrations, compared with normal

corn starch, in the Zucker diabetic fatty rat, an obese model of T2D (78). Furthermore, RS led to an improvement in renal histopathological score, suggesting a renoprotective effect in the setting of diabetes (78). In a rat model of adenine-induced CKD, a diet containing 59% high-amylose maize starch led to improvements in creatinine clearance, serum creatinine, renal inflammation, and interstitial fibrosis, compared with animals fed a low-fiber diet containing 12.8% cellulose (79). Limited research has been completed in humans, with a 2014 study finding no difference in albuminuria or blood urea concentrations after 6 wk of RS supplementation; however, there were marked reductions in uremic retention solutes, as discussed below (80). This study provided RS as a powder in sachets and instructed patients to mix the supplements in with food and drinks, with the placebo group receiving sachets containing highly digestible corn starch (80). A recent study showed that after 8 wk of RS supplementation, provided as biscuits, hemodialysis patients had no change in albuminuria; however, there were reductions in serum urea, creatinine, IL-6, and TNF-α concentrations (81). The placebo in this study consisted of biscuits prepared using regular wheat flour. The evidence from animal and human studies using RS in the context of CKD is summarized in **Table 2**. Whereas there is a paucity of evidence in humans for the use of RS to ameliorate CKD, results from animal trials are promising and suggest that it would be beneficial to trial longer-duration studies in humans.

RS and the Microbiome

It is generally accepted that dietary fibers, including RS, are able to modify the gut microbiota by acting as a digestible substrate to be utilized by the saccharolytic bacteria of the colon. Results from animal studies have shown that RS supplementation increases abundance of *Bacteroides* (83, 84), *Bifidobacteria* (74, 83–87), and *Lactobacilli* (84, 86–88). However, not all studies have shown this effect, with 2 wk, 8 wk, or 6 mo of feeding RS (9% potato starch) having no effect on *Lactobacilli* (89). Human studies have shown that RS supplementation increases abundance of *Bifidobacteria* (90, 91) and a double-blind crossover study in 10 healthy humans showed that 3 wk of supplementation with RS4, although not RS2, was associated with an increase in Bacteroidetes and a decrease in Firmicutes, suggesting that different types of RS may have functional differences in how they affect the human gut microbiota (92). The general consensus among the scientific literature is that RS supplementation is associated with increases of *Bifidobacteria* and *Lactobacilli*.

Further research using 16S ribosomal RNA sequencing has identified particular bacterial species that are affected by RS feeding. Kalmokoff et al. (74) showed that, in rats, RS2 increases *Bacteroides uniformis* concentrations. Interestingly, RS4 feeding in humans has also been associated with an increase in *B. uniformis* (93). Another species that has been shown to be upregulated with RS in humans is *Eubacterium rectale* (92, 94, 95), a well-recognized butyrate producer (96). Several studies have shown that *Ruminococcus bromii* is increased with RS supplementation in animals (74, 97, 98) and humans (92, 94, 99, 100). Recent genetic analyses demonstrate that *R. bromii* has a unique, specialized organization of extracellular amylases that give it an exceptional ability to ferment RS (101), suggesting it may be a "keystone" species for the degradation of RS (102). *R. bromii* is not a butyrate producer; however, it was recently shown that *R. bromii* may promote the growth of *Anaerostipes hadrus*, which is not a starch degrader but is a butyrate producer (103). Although the specific mechanism is still under investigation, it is known that RS supplementation affects the microbiota by promoting the selective growth of certain bacterial species.

Although it is known that patients with CKD have an altered microbiota, and that RS promotes the growth of beneficial bacteria, there is a paucity of studies that have specifically looked at the effects of RS on the microbiota in the context of CKD. Kieffer et al. (82) utilized the adenine-induced Sprague-Dawley rat as a model of CKD and found that RS supplementation altered bacterial composition, notably by a decrease in the Firmicutes phylum, an increase in the Bacteroidetes-to-Firmicutes ratio, and increases in *Bifidobacteria*. A study in healthy rats supplemented with 5% RS reported changes in the gut microbiota, notably increases in Bacteroidetes, *Bifidobacteria*, *R. bromii,* Porphyromonadaceae, and *B. uniformis* that were associated with a decrease in blood urea nitrogen concentrations, which may give us some indication of effects on renal function, outside of the context of CKD (74). Although there is growing consensus that RS represents a potential therapeutic avenue to target the microbiota of patients with CKD (**Figure 1**), there is a lack of evidence, particularly in human trials, that RS alters the microbiome in the context of CKD. The authors note that researchers at the University of Arkansas have recently registered a clinical trial (NCT03356990) that will hopefully shed further light on this question.

RS and SCFAs

SCFAs are carboxylic acids containing two- to six-carbon molecules that are naturally produced in small quantities in the liver, but their primary site of production is in the colon by specific gut microbiota. Acetate (C2), propionate (C3), and butyrate (C4) are the major SCFAs generated through bacterial fermentation of dietary fibers and are released in the proximal colon in high concentrations (70–140 mM), whereas their concentrations are lower in the distal colon (20–70 mM) and the distal ileum (20–40 mM) (104). Butyrate is primarily utilized locally by colonocytes, whereas small concentrations of propionate and acetate travel through the portal vein to the liver, where propionate is metabolized by hepatocytes and acetate is utilized by the liver and released to peripheral tissues (25). The ability of SCFAs to alter gene expression through histone deacetylase inhibition and activation of G-protein coupled receptors (GPCRs), including GPR41, GPR43, GPR109a, and olfactory receptor 78 (Olfr78), throughout the body makes them

TABLE 2 Summary of trials using RS interventions and measuring renal parameters[1]

Study (reference)	Intervention	Population	Group size, *n*	Study duration	Albuminuria	CrCl	BUN	Nitrogen		Cecal NH_4	Plasma		Other findings
								Urinary	Fecal		IS	PCS	
Healthy animals													
Kalmokoff et al. (74)	5% HAMSRS2 vs. cellulose	Male BioBreeding control rats	8	4 wk	—	—	↓	—	—	—	—	—	—
Younes et al. (75)	25% RS (crude potato starch) vs. digestible starch	Male Wistar rats	10	3 wk	—	—	↓	↓	↑	↓	—	—	↑ urea transferred to cecum, ↑ nitrogen balance
Diabetic animals													
Koh et al. (77)	5%, 10%, or 20% HAMSRS2-supplemented diet vs. normal corn starch	Male STZ-induced T1D SD rats	8	4 wk	↔	↔	—	—	—	—	—	—	
Koh et al. (78)	20% HAMSRS2-supplemented diet vs. normal corn starch	Male Zucker diabetic fatty rats	8	6 wk	↓	—	—	—	—	—	—	—	↓ renal histopathology scores ↓ kidney weight
CKD animals													
Younes et al. (76)	20% RS (crude potato starch) vs. fiber-free diet	Unilateral nephrectomized male Wistar rats	10	17 d	—	—	↓	↓	↑	↓	—	—	
Vaziri et al. (79)[2]	59% HAMSRS2 vs. low fiber	Adenine-induced CKD male SD rats	9	3 wk	↓	↑	↔	—	—	—	—	—	↓ interstitial fibrosis ↓ renal NF-κB p65, MCP-1
Kieffer et al. (82)[2]	59% HAMSRS2 vs. low fiber	Adenine-induced CKD male SD rats	9	3 wk	—	—	—	—	—	—	↓	—	↓ urinary IS, p-cresol, hippurate ↑ serum IAA, ↓ serum uric acid
Human studies													
Sirich et al. (80)	15–30 g/d HAMSRS2 vs. control starch	HD patients (male and female)	20	6 wk	↔	—	↔	—	—	—	↓	↓	
Tayebi Khosroshahi et al. (81)	20–25 g/d HAMSRS2 vs. regular wheat flour biscuits	HD patients (male and female)	22	8 wk	↔	—	↓	—	—	—	—	—	↓ serum creatinine ↓ serum uric acid

[1] BUN, blood urea nitrogen; CKD, chronic kidney disease; CrCl, creatinine clearance; HAMS, high-amylose maize starch; HD, hemodialysis; IAA, indole acetic acid; IS, indoxyl sulfate; MCP-1, monocyte chemoattractant protein 1; PCS, p-cresyl sulfate; RS, resistant starch; SD, Sprague-Dawley; STZ, streptozotocin; T1D, type 1 diabetes; ↑, increased; ↓, decreased; ↔, no change; —, not reported.
[2] Using the same cohort.

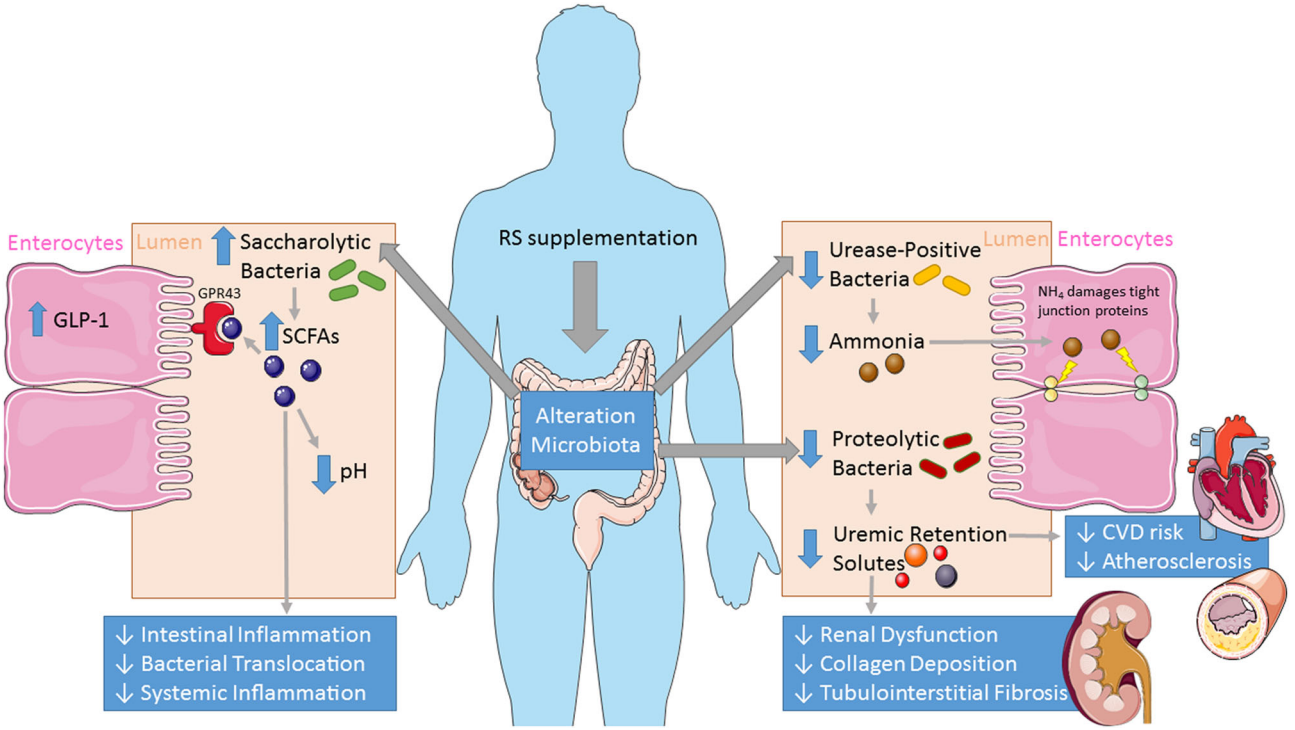

FIGURE 1 Effects of RS on the gut microbiota and microbial metabolites. Blue arrows indicate the effects of RS. CVD, cardiovascular disease; GLP, glucagon-like peptide; GPR43, G-protein-coupled receptor 43; RS, resistant starch.

important mediators in multiple cellular and molecular processes involving immunity, inflammation, glucose and lipid metabolism, and gastrointestinal health (105).

Animal studies have shown that RS feeding increases cecal concentrations of SCFAs in rats (87, 88, 106–108) and pigs (86, 98). RS supplementation increases fecal SCFA concentrations in rats (74, 87), pigs (109), and humans (93, 99, 110, 111). Results from animal (83, 89) and human (100, 110) studies have indicated that RS feeding is associated particularly with production of butyrate, with less of an effect seen on propionate concentrations. However, the effect of RS on particular SCFAs has been inconsistent, with 1 study finding increases in propionate, but neither acetate nor butyrate, concentrations in the distal colon of rats (97); another study finding increases in propionate and acetate, but not butyrate, in the cecum and colon of pigs (98); whereas another study in rats showed increases in acetate but not propionate or butyrate (85). Historically there has been a lack of standardized methodology for the measurement of SCFAs, which may account for some of the inconsistencies between studies. Recent advances in stable-isotope techniques may provide some clarity (112). Production of SCFAs by gut microbial fermentation of RS lowers the pH of the cecum (107) and colon (86, 99, 106), favoring the proliferation of saccharolytic bacteria. The general consensus is that RS feeding increases the production of butyrate, which can occur from direct fermentation by butyrate-producing species, such as *E. rectale* (113), or indirectly by cross-feeding between members of the gut microbiome (114). For example, *Bifidobacteria* lack the enzymes for butyrate production but ferment RS to produce substrates that are metabolized by butyrate-producing colon bacteria (115). SCFAs have been shown to mediate anti-inflammatory effects (116) and it is suggested that improvements in renal function can be attributed, in part, to RS promoting the proliferation of SCFA-producing bacteria and the subsequent rise in SCFA concentrations mediating the attenuation of the inflammatory sequelae (79).

Glucagon-like peptide 1

Engagement of GPR43 by SCFAs stimulates the secretion of the incretin hormone glucagon-like peptide 1 (GLP-1) from intestinal L cells. GLP-1 has been shown to be protective against diabetic nephropathy, by inhibiting NAD(P)H oxidase and subsequently reducing renal oxidative stress (117). GLP-1 also dose-dependently stimulates natriuresis and the renal excretion of other electrolytes such as calcium, phosphate, and chloride (118, 119). In animal studies, GLP-1 attenuates hypertension induced by angiotensin II, the main effector hormone of the renin–angiotensin system, by blockade of angiotensin II–induced superoxide formation (120, 121), and enhances glucose-stimulated insulin secretion from pancreatic β cells and inhibits glucagon release from α cells, which reduces hepatic glycogenolysis and enhances peripheral glucose uptake (122). Animal models have shown an increase in serum GLP-1 with RS supplementation (123–126); however, no such changes have been detected in human trials (56, 65).

Metabolic endotoxemia

LPSs are endotoxins found in the cell membrane of gram-negative bacteria. Upon entry into the bloodstream from the gut within chylomicrons, LPS activates a proinflammatory cascade by binding to the Toll-like receptor-4 on macrophages and monocytes. This promotes the transcription of cytokines, chemokines, adhesion molecules, and reactive oxygen species (ROS), resulting in low-grade chronic inflammation, enhanced oxidative stress, and insulin resistance (127). Increased concentrations of LPS in the circulation have been referred to as "metabolic endotoxemia," which is observed in people with obesity, insulin resistance, T2D, and CKD (128, 129). Feeding of dietary prebiotics, and the subsequent production of SCFAs, has been shown to reduce metabolic endotoxemia by maintaining the integrity of the gastrointestinal barrier. SCFAs upregulate the production of intestinal glucagon-like peptide 2 (GLP-2), tight-junction proteins (occludin, zonula occludens-1), and intectin, which together reinforce the health and structure of the intestinal endothelium and maintain optimal gut permeability (130, 131). GLP-2 also upregulates the transcription of tight-junction proteins (claudins, occludins), which connect the actin cytoskeletons of adjacent colonocytes (132, 133). Butyrate upregulates the mucin-associated genes responsible for generating production of the thick mucin layer that plays an important role in maintaining the integrity of the intestinal mucosal barrier (134). Modification of gut microbial composition, gastrointestinal permeability, or chylomicron absorption could have future applications in preventing the progression of CKD.

Although the majority of studies investigating the effects of RS on the production of proinflammatory cytokines have been performed in rodents, a few RS supplementation studies conducted in humans with T2D demonstrated significant reductions in TNF-α (65, 68) and IL-6 (68) and increased total antioxidant capacity (70). However, an equal number of trials found no effect of RS on inflammatory markers in healthy or overweight individuals (53, 71, 135).

Regulatory T cells

Regulatory T cells (Tregs) are suppressive lymphocytes, which prevent excessive immune responses to foreign antigens in order to prevent autoimmune activation (136). Butyrate enhances the number and function of Tregs and has ameliorated a number of autoimmune inflammatory conditions in mice (137). People with ESRD have lower quantities of Tregs due to elevated urea concentrations in the circulation, and excessive oxidative stress may induce early cell-cycle arrest and premature apoptosis of Tregs (138, 139). In the absence of Treg-induced immune cell suppression, inappropriate T cell responses in people with CKD can result in renal tissue injury, hypersensitivity reactions, and glomerulonephritis (140). RS supplementation has been shown to increase expansion of Tregs and reduce inflammatory injury in mouse models of colitis (141) and inflammatory bowel disease (142). GPR109a is highly expressed in adipocytes, intestinal epithelial cells, dendritic cells, and macrophages (143) and engagement of butyrate with GPR109a receptors on immune cells stimulates the production of the anti-inflammatory cytokine IL-10, which supports the production of Tregs from naïve T cells while repressing the generation of proinflammatory T-helper (Th) 17 cells (144). The use of RS to increase colonic SCFA production and encourage the expansion of Tregs represents a potential therapeutic mechanism for the restoration of immune homeostasis and reduction of renal injury in the context of CKD.

RS and Uremic Retention Solutes

We have already discussed that RS may have beneficial effects in CKD by promoting bacteria that produce health-promoting metabolites (i.e., SCFAs); it is also recognized that RS may assist in decreasing nitrogenous loads and the concentrations of nitrogenous compounds that accumulate in patients with CKD.

Urea and ammonia

Urea accumulates in the blood of patients with kidney disease due to insufficient renal excretion, translocates into the intestinal lumen, and is associated with an increase in the population of urease-positive bacteria (145), which convert urea into ammonia, altering intestinal pH (146). Ammonia degrades the tight epithelial junctions of the gut, leading to bacterial translocation from the gut lumen into the systemic circulation, which stimulates an inflammatory response that is thought to contribute to the progression of CKD (147, 148). Hemodialysis patients have elevated circulating IL-6, high-sensitivity C-reactive protein, and endotoxin concentrations compared with controls (149); and gut-derived microbial DNA has been detected in the circulation of patients with CKD (150). Andersen et al. (151) utilized a Col4α3-deficient mouse model of CKD (Alport nephropathy) to demonstrate that uremic mice had elevated endotoxin concentrations, which were accompanied by alterations in the gut microbiota and activation of splenic T lymphocytes. When antibiotics were used to eradicate facultative anaerobic microbes in mice with CKD, markers of systemic inflammation were reduced to the same levels as those seen in nonuremic mice, highlighting a crucial role for the microbiome linking uremia and inflammation (151).

RS supplementation decreases plasma urea concentrations associated with increases in fecal nitrogen excretion in rats (75, 76) and humans (152, 153). Dietary intake of fermentable fibers increases fecal bacterial mass and nitrogen output while decreasing blood urea nitrogen concentrations (154), suggesting that the decrease in plasma urea seen with RS supplementation is due to nitrogen being utilized for microbial growth. In hemodialysis patients, 8-wk supplementation with RS was associated with a decrease in uremia, an effect that was not seen after 4 or 6 wk (80, 81). During CKD there is an increase in the number of urease-positive bacteria and a decrease in saccharolytic bacteria (14) and RS has been shown to decrease cecal ammonia concentrations (75, 84) while increasing the relative abundance of saccharolytic

bacteria (74, 85). It has been suggested that this increase in saccharolytic bacteria causes competitive colonization of the colon that attenuates the number of urease-possessing bacteria (155). Targeting the gut microbiota with RS may prevent or slow CKD progression by altering the abundance of microbial communities that produce nitrogenous waste compounds.

P-cresyl sulfate and indoxyl sulfate

Two of the most well-studied uremic retention solutes, p-cresyl sulfate (PCS) and indoxyl sulfate (IS), are formed from dietary amino acids by colonic bacteria that possess p-cresol– and indole-forming enzymes, respectively. Wikoff et al. (156) used a targeted MS metabolomics screening to reveal that many protein-bound uremic toxins were dependent on the presence of the gut microbiota. The colonic source of these microbial metabolites has also been confirmed in hemodialysis patients who had undergone colectomy; these metabolites were significantly lowered compared with patients with an intact colon (157). There is an increase in serum IS and PCS in patients with CKD due to an increase in the bacterial populations that produce these toxic metabolites (14, 158) in tandem with a reduction in renal clearance (159). Furthermore, these compounds bind to albumin in the blood, limiting removal during hemodialysis (160). Both IS and PCS are associated with the progression of CKD (161) and with inflammatory markers in CKD patients (162), and serum concentrations of these uremic toxins have been shown to predict the progression of nephropathy (163).

Serum PCS concentrations are predictive of coronary artery disease in patients with diabetic nephropathy (164) and multiple studies have shown that plasma PCS is an independent predictor of CVD and mortality in hemodialysis (165–167) and predialysis CKD (168) patients. The association between plasma PCS and mortality in CKD patients has been confirmed in a recent meta-analysis (169). A nested case-control study performed a metabolomics screen of patients with T2D and found that those who progressed to ESRD had higher baseline plasma PCS, but not IS, than those who did not (170). In CKD patients not yet requiring dialysis, serum concentrations of p-cresol, the precursor to PCS, were shown to predict cardiovascular events, independently of kidney function or Framingham risk score (171). Urinary PCS has also been reported to independently predict cardiovascular events in patients with mild to moderate CKD (172). Mechanistically, PCS increases the expression of inflammatory genes (173), impairs mitochondrial function (174), and promotes epithelial-to-mesenchymal transition (175) in renal proximal tubular cells. PCS has a proapoptotic and proinflammatory effect on human proximal tubular epithelial cells (176); has been shown to increase oxidative stress in leukocytes (177), cardiomyocytes (178), endothelial cells, and smooth muscle cells (179, 180); and in vivo superfusion at uremic concentrations increases the number of rolling leukocytes on the vascular endothelium (181). In vitro PCS has been shown to suppress the immune response of Th1 cells (182) and alter macrophage cytokine production in response to LPS, with an increase in IL-10 production (183). Work in animal models has identified enhanced NAD(P)H oxidase activity leading to increased oxidative stress and subsequent induction of inflammatory cytokines that contribute to renal fibrosis (184); and in vitro knockdown of Nox4, an NAD(P)H oxidase isoform, ameliorates PCS-induced ROS production and monocyte chemoattractant protein 1 (*MCP-1*) expression (180).

Serum IS concentrations are associated with coronary atherosclerosis (185), coronary artery disease (164), heart failure (186), and all-cause mortality (187) and are a predictor of CVD (188) and cardiovascular mortality (189) in CKD patients. IS promotes CKD progression (190) and chronic IS exposure in mice is associated with worsening glomerulosclerosis (191) and an increase in the urinary albumin-to-creatinine ratio (192). In vitro studies have demonstrated that IS induces ROS production (193, 194), which contributes to endoplasmic reticulum stress (195), oxidative stress (196, 197), and activation of the NF-κB pathway leading to increased expression of profibrotic genes in proximal tubular cells (198) and intercellular adhesion molecule 1 (*ICAM-1*) and *MCP-1* in vascular endothelial cells (199). Furthermore, this NF-κB activation leads to the production of proinflammatory cytokines, leading to increased macrophage infiltration into the kidneys of rats (200), and IS has been shown in vitro to promote TNF-α and IL-1β production by THP-1–derived macrophages (201). IS promotes epithelial-to-mesenchymal transition in vitro in renal proximal tubular cells (175, 202, 203) and in vivo in a hypertensive rat model (203). In vitro and in vivo studies have demonstrated that mitochondrial function is impaired by IS, which may be ameliorated by antioxidants that reduce oxidative stress (174, 204). IS acts as a ligand for the aryl hydrocarbon receptor (AhR) (205), a transcriptional factor that regulates inflammation, detoxification, and carcinogenesis (206). AhR is expressed by mouse podocytes (192, 207) and in vitro exposure of mouse podocytes to IS increases proinflammatory gene expression and decreases cell viability (192).

Targeting the microbiota to reduce uremic retention solutes

Given the pathogenic effect of uremic retention solutes, there has been significant interest in the use of dietary therapeutic interventions to alter the microbiome and alter the concentrations of these metabolites of microbial origin (208, 209). A cross-sectional study in patients with stage 4–5 CKD found that dietary fiber intake was inversely associated with serum PCS (210) and interventional human studies demonstrate that prebiotic fibers targeting the gut microbiota reduce urinary (211, 212) and plasma PCS (213, 214) concentrations. In mice that had undergone a five-sixths nephrectomy, arabino-xylo-oligosaccharide reduced PCS concentrations and insulin resistance (215), whereas galacto-oligosaccharide reduced indole-positive bacteria, serum IS, tubulointerstitial injury, and tubular ER stress and apoptosis (216). Synbiotics (combinations of pre- and probiotics) trials

in human populations have shown beneficial effects and reduced plasma concentrations of p-cresol (217, 218) and PCS (219). Those trials that did measure IS showed no change with synbiotic treatment (218, 219), suggesting that these uremic toxins may be regulated by different pathways. There is limited evidence to indicate that probiotics by themselves play a role in reducing uremic toxins—this is covered in a recent review by Briskey et al. (220). Feeding rats with adenine-induced CKD an RS2-supplemented diet decreases proteinuria, albeit not to the level of controls (79), and a follow-up study using an untargeted metabolomics screen demonstrated that RS was associated with a decrease in serum IS and p-cresol (103). In healthy volunteers, RS supplementation significantly reduced fecal concentrations of p-cresol, although no change was observed in urinary p-cresol concentrations (153); and more recently, Sirich et al. (80) demonstrated RS supplementation in hemodialysis patients decreased IS and PCS. These data indicate that nondigestible carbohydrates, including RSs, may play an important role in retarding CKD progression by limiting the production of uremic retention solutes.

Emerging uremic retention solutes

Although most of the research to date has been focused on the uremic retention solutes PCS and IS, a total of 88 chemicals have been identified that are deemed uremic retention solutes (221), some of which may play a role in CKD development. This increased rate of discovery of uremic retention solutes has been ascribed to the implementation of newer technologies which have improved sensitivity for detecting metabolites (222). Furthermore, the production of several of these retention solutes has been shown to be dependent on the gut microbiota (156), indicating that dietary interventions that alter the microbiome may represent a potential therapeutic strategy in CKD.

Phenylalanine metabolites

Dietary phenylalanine is able to be converted by the gut microbiota into a variety of products that may have implications for kidney disease. Decarboxylation of phenylalanine produces phenylethylamine, a reaction that is catalyzed by the enzyme tyrosine decarboxylase (223), which is present in gram-positive bacteria and has been found to be particularly prevalent among lactic acid bacteria (224). The majority of phenylethylamine undergoes oxidation to form phenylacetic acid (225), which is increased in the plasma of patients with ESRD (221, 226). In vitro work has shown that phenylacetic acid increases ROS formation (227), impairs mitochondrial metabolism (228), and can directly inhibit renal tubular efflux pumps (229). Another microbial pathway for phenylalanine leads to the production of m-tyramine, which undergoes further enzymatic conversion to 3-hydroxyphenylacetic acid (230), which is elevated in the plasma of hemodialysis patients (231). Presence of phenylacetic acid in plasma is dependent on the gut microbiota (156) and rats with adenine-induced CKD receiving an RS-supplemented diet had reductions in the concentration of 3-hydroxyphenylacetic acid by 71% in cecal digesta and 64% in the serum (103), suggesting that targeting of the gut microbiota may prove a useful therapy.

Phenylacetic acid undergoes hepatorenal glutamine conjugation to form phenylacetylglutamine (PAG) (232). Serum PAG concentrations are >100 times higher in hemodialysis patients than in healthy volunteers (233), inversely associated with estimated glomerular filtration rate (GFR) in a healthy population (234), positively associated with progression to ESRD in patients with diabetes (170), and associated with risk of CVD in predialytic (235) and dialysis-requiring (236) CKD patients. Serum concentrations of PAG were 14 times greater in dialysis patients with an intact colon than in those who had undergone a colectomy, demonstrating the role of the microbiota in the production of PAG (157), and PAG concentrations have been shown to correlate with the relative abundance of bacterial families from the Clostridiales order (235). It remains unclear whether PAG is a uremic toxin per se (235) as it undergoes tubular secretion (237), and elevated PAG concentrations may be reflective of increased tubular dysfunction. It is known that the products of the microbial metabolism of phenylalanine are increased in patients with CKD, and animal studies show these are reduced with RS supplementation; however, further studies are required to assess the clinical implications of these findings.

Hippurate

Dietary aromatic compounds are metabolized by the gut microbiota, forming benzoates that undergo hepatorenal conjugation with glycine, leading to the formation of hippurate (11). Patients with ESRD have plasma concentrations of hippurate that are >100 times higher than those of healthy controls (233). Hippurate can directly inhibit renal tubular efflux transporters (229), and in rats that had undergone a subtotal nephrectomy, 18 wk of treatment with 500 mg hippurate $\cdot$ kg^{-1} $\cdot$ d^{-1} in drinking water induced a reduction in GFR and an increase in glomerulosclerotic index (238). ROS production was observed when endothelial cells were treated with hippurate in the absence of albumin; however, this was not observed when albumin was present, suggesting that this effect may not be physiologically relevant (193). Furthermore, plasma hippurate concentrations were not associated with progression to ESRD in a cohort with T2D (170), nor did they correlate with CVD risk in dialysis patients (236). Results from animal studies indicate the gut microbiota is required for the production of hippurate (156) and adenine-induced CKD rats fed with RS had a 74% reduction in the urinary concentration of hippurate (103). However, there was no difference in plasma concentrations of hippurate between dialysis patients with and without a colon (157), and it is suggested that the majority of hippurate in humans may come from precursors that are absorbed in the small intestine (239). Reduced clearance of hippurate is associated with an increased risk of mortality independent

of estimated GFR in a population with CKD not requiring dialysis (240); however, given that hippurate is cleared by tubular secretion, this may simply be a marker of tubular dysfunction. The role of hippurate in the progression of kidney disease is unclear; however, it may be an interesting metabolite to consider including in future studies looking at the gut–kidney axis.

Tryptophan metabolites

The most widely studied product of microbial tryptophan metabolism is IS, a well-established nephrotoxic compound that is formed by production of indole from tryptophan by tryptophanase-expressing bacteria and that is conjugated to sulfate in the liver (discussed in detail above). Bacterial metabolism of tryptophan may undertake other routes to produce compounds such as indole acetic acid (IAA), another protein-bound uremic retention solute (241). Serum IAA concentrations are increased in CKD populations, correlate with worsening stage of disease (242), and predict mortality and CVD in patients with CKD (156, 242). In an animal model of CKD, treatment of IAA in drinking water contributed to a reduction in GFR (measured by inulin clearance), increased glomerulosclerosis, and interstitial fibrosis (238). Mechanistically, IAA has been shown to dose-dependently activate NF-κB and promote free radical production in human proximal tubule cells (197). IAA is able to activate AhR (241), which has been shown in vitro to increase expression of the proinflammatory cyclo-oxygenase 2 (COX-2) enzyme, activate NF-κB via p38 phosphorylation, and increase ROS production (242).

Interestingly, in a rat model of adenine-induced CKD, rats supplemented with RS had serum concentrations of IAA that were 615% higher than those of rats fed a low-fiber diet (103). Importantly, these rats had an improvement in creatinine clearance with RS feeding (79) despite these large increases in IAA, although it is important to note that RS reduced IS (103). In conventionally raised mice, the cecal concentration of indole is ~20 times greater than the concentration of IAA (243), and the composition of the gut microbiota plays an important role in determining the metabolites produced from microbial metabolism of tryptophan. One possible hypothesis, albeit one that requires experimental testing, is that RS supplementation alters the microbial composition, resulting in a "shunting" of tryptophan bacterial metabolism, resulting in greater IAA and less indole production, subsequently leading to lower IS production.

Trimethylamine-N-oxide

Trimethylamine-N-oxide (TMAO) is a uremic retention solute of microbial origin that has been implicated in CVD. Dietary phosphatidylcholine, primarily found in animal products including liver, eggs, milk, red meat, poultry, fish, and shellfish, is a major dietary source of choline (244), which undergoes deamination by the microbial enzyme choline trimethylamine lyase (CutC) to produce trimethylamine (245), which is oxidized by hepatic flavin monooxygenase (FMO) to produce circulating TMAO (246). Another dietary precursor to TMAO is L-carnitine, a nutrient found abundantly in red meat, which has a similar chemical structure to choline and also undergoes microbial metabolism to form trimethylamine (247). Wang et al. (248) undertook a metabolomics screen of >2000 compounds and found that TMAO, choline, and betaine (another TMAO precursor) were associated with CVD risk and the progression of atherosclerosis. TMAO is cleared by the kidneys and serum TMAO concentrations are elevated in patients with ESRD (249–251) and stage 3–4 CKD (252) and have recently been shown to correlate with renal function and inflammation in CKD patients (253). Plasma TMAO concentrations are a predictor of coronary atherosclerosis (254), CVD (255), and mortality (253, 254, 256) in CKD patients. Animal studies have shown that dietary supplementation of TMAO, or its precursor choline, is associated with increased serum TMAO concentrations, tubulointerstitial fibrosis, collagen deposition, SMAD3 phosphorylation, and progressive renal dysfunction (256). The gut microbiota plays an important role in TMAO production, with antibiotic treatment of mice preventing choline-induced increases in TMAO and atherosclerosis (248), and transplanting fecal samples from patients with CKD into antibiotic-treated mice increased TMAO concentrations (249). Given the important effect of TMAO on CKD and CVD, and the clear role that the gut microbiota plays in the production of TMAO, it may be prudent to investigate whether dietary interventions such as RS alleviate disease risk by alterations in TMAO concentrations.

To date, the authors are aware of no studies that have measured the effects of RS supplementation on TMAO concentrations in patients with CKD. Two recent studies have shown that 2-wk feeding of an RS-rich diet was associated with increases in plasma concentrations of TMAO in healthy (42) and insulin-resistant (95) individuals. Intriguingly, another study using a targeted metabolomics approach found that TMAO was one of the most increased metabolites after consumption of a low-glycemic-load diet (257). This is in contrast to epidemiologic studies that have found in men, but not women, that high-glycemic-load diets are associated with increased risk of CVD (258). Further research is required to determine whether the use of dietary carbohydrate sources that are associated with an increase in plasma TMAO concentrations translates to negative long-term cardiovascular consequences, particularly in the context of CKD.

Conclusions

In light of the increasing recognition of the role of microbial dysbiosis in the progression of CKD, there has been much interest in using dietary modification to favorably alter the microbiome of patients with CKD. RS is a prebiotic compound that is resistant to digestion by human α-amylases and becomes available for fermentation in the colon, favoring the proliferation of health-promoting bacteria including *Bifidobacteria* and *Lactobacilli*. This change in the microbiota is associated with an increase in SCFAs and a decrease in

uremic retention solutes that are produced by the microbiota. SCFAs confer health benefits by a number of mechanisms including ligating with metabolite-sensing GPCRs to promote GLP-1 secretion, promotion of gastrointestinal barrier integrity, and enhancing the number and function of Tregs. Uremic retention solutes are produced by the colonic flora, contribute to the progression of CKD, and are reduced by supplementation with RS. Recent research has identified a number of emerging gut-derived uremic retention solutes. Phenylacetic acid and phenylacetylglutamine are 2 products that arise from the microbial metabolism of the amino acid phenylalanine that are increased in CKD and reduced by RS supplementation. Hippurate concentrations are increased in patients with ESRD and reduced by RS; however, there is insufficient evidence for a causative role in CKD progression. IAA has been shown experimentally to contribute to the development of CKD; however, RS supplementation was associated with large increases in serum concentrations despite improvements in renal function. IAA and IS are both products of tryptophan metabolism, so a possible explanation is that RS shunts the tryptophan microbial metabolism pathway; however, this requires experimental testing. TMAO, a nephrotoxic compound of microbial origin, was increased in healthy volunteers after RS supplementation. Further research is required to elucidate the implications of RS supplementation relative to TMAO in the context of CKD. Diet is used as an adjunct therapy in CKD, and RS can be added to conventional foods to create functional foods that confer a health benefit. Overall, RS represents a promising avenue for providing therapeutic benefit to patients with CKD by targeting the microbiome.

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