Uremic toxins originating from colonic microbial metabolism

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Numerous molecules, which are either excreted or metabolized by the kidney, accumulate in patients with chronic kidney disease (CKD). These uremic retention molecules (URMs), contributing to the syndrome of uremia, may be classified according to their site of origin, that is, endogenous metabolism, microbial metabolism, or exogenous intake. It is increasingly recognized that bacterial metabolites, such as phenols, indoles, and amines, may contribute to uremic toxicity. *In vitro* studies have implicated bacterial URMs in CKD progression, cardiovascular disease, and bone and mineral disorders. Furthermore, several observational studies have demonstrated a link between serum levels of bacterial URMs and clinical outcomes. Bacterial metabolism may therefore be an important therapeutic target in CKD. There is evidence that besides reduced renal clearance, increased colonic generation and absorption explain the high levels of bacterial URMs in CKD. Factors promoting URM generation and absorption include an increased ratio of dietary protein to carbohydrate due to insufficient intake of fiber and/or reduced intestinal protein assimilation, as well as prolonged colonic transit time. Two main strategies exist to reduce bacterial URM levels: interventions that modulate intestinal bacterial growth (e.g., probiotics, prebiotics, dietary modification) and adsorbent therapies that bind bacterial URMs in the intestines to reduce their absorption (e.g., AST-120, sevelamer). The efficacy and clinical benefit of these strategies are currently an active area of interest.

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Chronic kidney disease (CKD) is a global health issue that has a substantial impact on affected individuals. Presenting symptoms of CKD are diverse and include, among others, the uremia syndrome. Uremia has recently been defined as 'those signs and symptoms accompanying CKD that cannot be explained by derangements in extracellular volume, inorganic ion concentrations, or lack of known renal synthetic products.'[1]

Loss of kidney function induces major alterations in the blood concentration of numerous molecules. In particular, substances that are either excreted or metabolized by the kidney accumulate as renal function declines, resulting in increased blood concentrations. These uremic retention molecules (URMs) constitute a long and ever-expanding list of molecules that substantially contribute to the syndrome of uremia.[1] A widely accepted classification, endorsed by the European Toxin Work Group, divides all known URMs into three groups, according to characteristics affecting their removal pattern during dialysis or other methods of extracorporeal elimination.[2] This physicochemical classification categorizes URMs into (1) small water-soluble molecules (<500 Da) that readily pass any dialysis filter; (2) larger molecules ($\geqslant 500$ Da), for which passage through a dialysis filter is limited and dependent on membrane characteristics (this group is often referred to as 'middle molecules'); and (3) protein-bound molecules, for which dialytic removal largely depends on the equilibrium between bound and free fractions, and for which adsorptive techniques might prove more efficacious.[3]

Alternatively, uremic retention solutes may be classified according to their origin, that is, endogenous metabolism, microbial metabolism, or exogenous intake (Table 1).[4–13] This classification system may prove valuable in the identification of therapeutic options beyond extracorporeal removal. Obviously, the majority of URMs originate endogenously from mammalian metabolism. It is, however, increasingly recognized that intestinal microbial metabolism also results in the generation of numerous URMs.[9] Finally, exogenous dietary URMs may also be an important additional source of URMs, such as oxalate[13] and advanced glycation end products[10,14] (see Vlassara *et al*. article in this supplement). This review focuses on URMs originating from colonic bacterial metabolism, which represent increasingly important targets in the treatment of uremia in CKD.

Table 1 | Uremic retention solutes implicated in cardiovascular disease and their source of origin

	Group	Endogenous metabolism	Microbiotic metabolism	Exogenous intake
ADMA[4]	Dimethylarginines	X		
p-Cresyl sulfate[5,6]	Phenols		X	
Phenyl acetic acid[7]	Phenols		X	
Indoxyl sulfate[8]	Indoles		X	
Indole 3-acetic acid[7,9]	Indoles		X	
AGEs[10,11]	NA	X		X
Homocysteine[12]	NA	X	X[a]	
Oxalate[13]	NA	X		X

ADMA, asymmetrical dimethylarginine; AGEs, advanced glycation end products; NA, not applicable.
[a]The colonic microbiota produce substantial amounts of folic acid, which in turn lower homocysteine concentrations.

BACTERIAL METABOLISM

The human large intestine is approximately 150 cm long, with an internal surface area of 1.3 m^2. It weighs approximately 220 g, of which 80% is moisture, and is slightly acidic with a pH of 6.0–7.0. The resident microbial community is complex, diverse, and biochemically very active. The slow transit of contents enables the development of large populations of bacteria (up to 10^{11}–10^{12} per gram content within the large intestine). These bacteria, which constitute 40–60% of the contents, belong to 400–500 different species. The predominant organisms are nonsporing, obligate anaerobes from the genera *Bacteroides*, *Fusobacterium*, *Eubacterium*, and *Bifidobacterium*. Many other bacteria occur in high numbers, including *Lactobacilli*, various anaerobic Gram-positive *Cocci*, and *Clostridia*.[15] The composition of an individual's colonic microbiota is considered to be fairly stable. Nevertheless, the dynamic equilibrium between species in the colon allows the flora to adapt metabolically to changes in the microenvironment, either by induction of enzymes or by alterations in the number or proportions of its constituent microorganisms.[16]

It has long been held that the principal role of the colon is to absorb salt and water, and to provide a mechanism for the orderly disposal of waste products of digestion. More recently, it has become clear that the colon is responsible for salvaging energy and possibly nitrogen from carbohydrate (CHO) and protein not digested in the upper gastrointestinal tract. This is achieved through the metabolism of anaerobic bacteria, a process known as fermentation.

Most research to date has focused on CHO fermentation in the large intestine. The end products formed include hydrogen, methane, and short-chain fatty acids such as butyrate, propionate, and acetate. Many of these end products, especially the latter, are generally accepted to be beneficial to the host.[17] Butyrate, for example, is metabolized by the colonic epithelium, which derives 60–70% of its energy from butyrate oxidation.

Protein fermentation (putrefaction), on the other hand, has been less extensively studied. On average, 0.3–4.1 g of nitrogen, the majority in the form of protein (50%) and peptides (20–30%), enters the colon daily.[18] These organic nitrogen compounds are degraded in several reaction steps. Initially, hydrolysis of the polypeptide chains by proteases and peptidases results in a mixture of small peptides and amino acids. Amino acids present in the colonic lumen are either used for bacterial growth or fermented to a variety of end products including short- or branched-chain fatty acids, and other metabolites, some of which are potentially toxic such as ammonia, amines, thiols, phenols, and indoles. Fermentation metabolites not used for bacterial protein synthesis accumulate in the colonic lumen, and are subsequently excreted in either feces or urine.[16,19,20]

FACTORS INFLUENCING BACTERIAL METABOLISM

Bacterial species are roughly categorized as saccharolytic (i.e., those that predominantly ferment CHO) or proteolytic (i.e., those that are predominantly protein fermenters) (Table 2).[13,21–26] At present, the mechanisms controlling bacterial metabolism are only partly understood. It is generally accepted that the most important regulator of bacterial metabolism is nutrient availability, especially the ratio of available CHO to nitrogen, which determines the degree of saccharolytic versus proteolytic fermentation.[27,28]

The amounts of nutrients entering the colon mainly depend on dietary intake and the efficiency of the assimilation process in the small intestine. Dietary CHO, which is resistant to digestion in the small intestine (i.e., resistant starch and dietary fibers or nonstarch polysaccharides), is the main source of CHO in the colon. Other CHO sources available for fermentation in lower concentrations include oligosaccharides and a variety of sugars and nonabsorbable sugar alcohols. Nitrogen is provided to the large intestine from dietary proteins that have escaped digestion in the upper gut, from endogenous proteins (e.g., pancreatic and intestinal secretions, or sloughed epithelial cells), and from blood urea that has diffused into intestinal contents. The colonic fate of α-amino nitrogen (amino acids and intermediates) largely depends on the amount of energy available for bacterial growth and cell division. The main source of energy is fermentable CHO. In cases of CHO excess, α-amino nitrogen is predominantly incorporated in the bacterial biomass. Conversely, in CHO deprivation, α-amino nitrogen is predominantly fermented, resulting in potentially toxic end products that may be absorbed to form bacterial URMs.

Along the length of the large intestine, the ratio of available CHO to nitrogen progressively declines, which

Table 2 | Studies with probiotic preparations in kidney disease

Study	Primary end point	*n*	Strain	Result
Hida *et al.*[21]	Indoxyl sulfate *p*-Cresol	20	Lactic acid bacilli (Lebenin)	−30% serum indoxyl sulfate No change serum *p*-cresol
Dunn *et al.*[22]	Dimethylamines	24	*Lactobacillus acidophilus*	−46% serum dimethylamine
Campieri *et al.*[23]	Urinary oxalate excretion	6	Lactic acid bacilli	−40% urinary oxalate excretion
Lieske *et al.*[24]	Urinary oxalate excretion	10	Lactic acid bacilli (Oxadrop)	−19% urinary oxalate excretion
Goldfarb *et al.*[13]	Urinary oxalate excretion	10[a]	Lactic acid bacilli (Oxadrop)	No significant changes
Takayama *et al.*[25]	Indoxyl sulfate	11	*Bifidobacterium longum* (Bifina)	−30% serum indoxyl sulfate
Taki *et al.*[26]	Indoxyl sulfate Homocysteine	27	*Bifidobacterium longum* (Bifina)	−9% serum indoxyl sulfate −13% plasma homocysteine

n, number of patients in active treatment arm.
[a]Randomized controlled trial.

impacts bacterial composition and metabolism.[29] Saccharolytic and proteolytic species predominate in the right colon and left colon, respectively.[15] Slowing down colonic transit times may induce an upstream expansion of proteolytic species, as a larger part of the colon becomes CHO deprived, resulting in an increased generation of bacterial toxins. In a landmark study by Cummings *et al.*,[20] a significant correlation was observed between longer colonic transit times and higher urinary excretion rates of phenols; 64% of the variance in the urinary excretion rate of phenols was explained by colonic transit time and dietary protein intake. Other factors that affect the fermentation process include age, drug treatment, local immunity, luminal pH,[30] and physicochemical properties of nutrients.[18]

BACTERIAL METABOLISM IN CKD

CKD influences several of the above-mentioned determinants of bacterial fermentation processes in the large intestine (i.e., ratio of CHO to protein, colonic transit time, and bacterial composition of intestines), which, combined with the dietary changes necessary for the management of CKD, create a potentially different intraluminal environment.

First, Kalantar-Zadeh *et al.*[31] observed that hemodialysis (HD) patients consumed significantly less dietary fiber as compared with control subjects (mean ± standard deviation (s.d.) intake: 12.4 ± 5.8 g/day vs 17.9 ± 10.6 g/day; $P = 0.02$). In this study, no difference in protein intake was noted. It can be hypothesized that prescribed restrictions in potassium in HD patients may lead to reduced fruit and vegetable ingestion and reduced dietary fiber intake.

Second, colonic transit times are prolonged in CKD. Indeed, constipation is frequent in maintenance dialysis patients. Whereas the prevalence of constipation ranges from 10 to 20% in healthy persons, rates as high as 63% in HD patients and 29% in those on continuous ambulatory peritoneal dialysis (CAPD) have been reported.[32] The cause of the greater prevalence of constipation in long-term HD patients seems to be multifactorial. Dialysis modality-based lifestyle, inactivity, phosphate binders, dietary restrictions, low fluid intake, primary renal disease (e.g., polycystic renal disease), and comorbidity including diabetes, cerebrovascular disease, heart failure, and malnutrition might all contribute to the greater prevalence of constipation in HD patients. Wu *et al.*[33] studied segmental and total colonic transit times by means of radio-opaque markers in 56 HD patients, 63 CAPD patients, and 25 healthy control subjects. Compared with healthy controls and CAPD patients, HD patients had a significantly longer mean colonic transit time (43.0 ± 22.2 h in HD patients, 32.7 ± 13.7 h in CAPD patients, and 24.3 ± 11.9 h in controls; $P < 0.001$). This increase in constipation will result in more time for bacterial production and intestinal absorption of URMs.

Third, several lines of evidence suggest that protein assimilation is impaired in uremia, and increased amounts of protein escape digestion and absorption in the small intestine.[34] The decreased ratio of available CHO to nitrogen may favor the proliferation of proteolytic species and generation of potentially toxic protein fermentation metabolites, such as phenols.

Finally, besides changes in nutrient availability and colonic transit time, blood ammonia concentrations (through modifying luminal pH) and drug therapy (e.g., phosphate binders, antibiotics, antimetabolites) should be considered as factors potentially modifying colonic microbiota and metabolism in CKD. Hida *et al.*[21] studied the colonic composition of microbiota in healthy controls and HD patients by examining fecal samples. A significant difference in the total number of bacteria could not be demonstrated. However, when considering individual species, several quantitative and qualitative changes were observed. The number of aerobic bacteria such as *Enterobacteria* and *Enterococci* was approximately 100 times higher in HD patients. Of the anaerobic bacteria, the number of *Bifidobacteria* was significantly decreased, whereas *Clostridium perfringens* were more abundant in HD patients. How well fecal samples reflect the composition of microbiota of the (left and right) colon is highly debatable.

Despite the identification of factors that may increase bacterial URMs, there are few studies evaluating the generation of fermentation metabolites in uremia. We quantified the 24-h urinary excretion of *p*-cresol, a prototype of the URM originating from protein fermentation, in a cohort of 88 patients with CKD. Significantly higher urinary *p*-cresol excretion was observed in subjects with glomerular filtration rate < 60 ml/min per 1.73 m^2 than in those with glomerular filtration rate $\geqslant 60$ ml/min per 1.73 m^2.[34] In

agreement with previous data, the colonic production of *p*-cresol was shown to correlate with dietary protein intake.[6] Moreover, after normalization for dietary protein intake, the stepwise increase of urinary *p*-cresol output, along with renal function impairment, was even more striking.[34]

PROTEIN FERMENTATION METABOLITES

Protein fermentation results in the generation of a complex array of different metabolites, including *p*-cresol, indole, and phenylacetic acid. Besides their common origin, some of these compounds share other features such as detoxification by conjugation and extensive protein binding.[3,35] Owing to their protein binding, elimination occurs mainly by tubular secretion through the organic anion transport system.[36] Whether significant extrarenal clearance occurs is hitherto unknown. This review focuses on phenols, indoles, and amines, which are the key bacterial URMs that have been studied in CKD.

Phenols

Phenolic compounds such as phenylacetic acid, phenol, and *p*-cresol are generated by the partial breakdown of tyrosine and phenylalanine by a wide range of intestinal obligate or facultative anaerobes, including the genera *Bacteroides*, *Lactobacillus*, *Enterobacter*, *Bifidobacterium*, and especially *Clostridium*.[17] However, complete breakdown of aromatic amino acids by colonic microbiota is limited. This process is thermodynamically unfavorable in the absence of an inorganic electron acceptor and can only occur to a significant degree under aerobic conditions, when mono- and dioxygenases can incorporate molecular oxygen into the reactants. *p*-Cresol is the most thoroughly studied representative of phenolic compounds. Most of the phenols produced in the colon are rapidly absorbed and detoxified by sulfate (and to a much lesser extent glucuronide) conjugation in the liver or colonic mucosa.[5]

Indoles

The bacterial metabolism of tryptophan in the colon results in the production of a wide range of indolic compounds. Intestinal bacteria such as *Escherichia coli* have tryptophanase that converts tryptophan to indole, which is quantitatively the major end product. Indoles are absorbed and metabolized to indoxyl sulfate in the liver.[17]

Amines

Decarboxylation of lysine and ornithine results in the production of polyamines cadaverine and putrescine. Breakdown of polyamines may give rise to simple amines.[30] Amines are rapidly absorbed from the colon and detoxified by monoamine and diamine oxidases in the liver or colon mucosa (to NH_3 and CO_2). However, some amines are also excreted in urine, including the heterocyclic products of putrescine and cadaverine oxidative deamination (i.e., pyrrolidine and piperidine). Aromatic amines are detoxified by conjugation.

UREMIC TOXICITY

All the above-mentioned protein fermentation metabolites accumulate as renal function deteriorates and may contribute to the uremic syndrome. To be classified as a uremic toxin, a URM should satisfy the following criteria: (1) it should be chemically identified and accurately quantifiable in biologic fluids; (2) its concentration in tissue or plasma from uremic subjects should exceed that present in nonuremic subjects; (3) toxic effects of the compound in a test system should be demonstrable at concentrations found in tissue or fluids from uremic patients; and (4) its concentration should correlate with specific uremic symptoms that disappear when the concentration is reduced to normal.

It should be noted that these criteria have rarely been met by any URMs, including those originating from protein fermentation.[37] This is mainly because of a lack of effective purification techniques. Rather than discussing the toxicity profile of the individual toxins, current knowledge on the role of protein fermentation metabolites in the progression of renal failure and in the pathogenesis of accelerated cardiovascular disease and uremic bone disease is summarized. The fact that survival time of anephric, germ-free rats is nearly twice that of conventionally raised rats underscores the importance of intestinal microbiota and metabolites in uremia.[38]

Protein fermentation metabolites and CKD progression

Niwa *et al.* first proposed that metabolites originating from bacterial protein fermentation in the large intestine have key effects in the progression of CKD.[8,39,40] Administration of indoxyl sulfate and its precursor, indole, to 5/6th nephrectomized rats increased glomerular sclerosis in the remnant kidney, with a decline in renal function.[10,14,41] Furthermore, indoxyl sulfate stimulated transcription of genes related to renal fibrosis, such as transforming growth factor-β1, tissue inhibitor of metalloproteinases-1, and pro-l collagen.[39,42] The induction of nephrotoxicity by indoxyl sulfate is mediated by organic anion transporters (OATs) such as OAT types 1 and 3 in the basolateral membrane of renal proximal tubular cells.[43] Indoxyl sulfate induces free radical production by renal tubular cells, and activates nuclear factor-κB, which, in turn, upregulates the expression of plasminogen activator inhibitor-1.[44] The free radical species produced in cells stimulated by indoxyl sulfate have been identified as hydroxyl radicals.[44] Recently, Gelasco and Raymond[45] reported that indoxyl sulfate augments extracellular superoxide dismutase-sensitive O_2 production and intracellular hydroxyl radical production in mesangial cells. Several smaller studies have suggested that reducing serum indoxyl sulfate concentrations slows CKD progression.[8,46] An ongoing, large multicenter trial is testing this hypothesis.[47] It is unknown whether this toxic effect is shared by other protein fermentation metabolites.

Protein fermentation metabolites and cardiovascular disease

Protein fermentation metabolites may be involved in the pathogenesis of accelerated cardiovascular disease in CKD.

Indoxyl sulfate and *p*-cresol inhibit endothelial proliferation and wound repair.[48] Faure *et al.* have shown that indoxyl sulfate and *p*-cresol induce shedding of endothelial microparticles *in vitro*,[49] which in turn is associated with endothelial dysfunction in patients with end-stage renal failure.[50] Recently, indoxyl sulfate was reported to stimulate proliferation of rat vascular smooth muscle cells,[51] and to promote vascular calcification and aortic wall thickening.[41] These *in vitro* experiments suggest that *p*-cresol and indoxyl sulfate may have a role in the dysfunction of endothelial and vascular smooth muscle cells in patients with CKD. It is noteworthy that several groups have independently demonstrated that *in vivo p*-cresol largely circulates in the form of its conjugate *p*-cresyl sulfate.[5,52] The effects of *p*-cresol and *p*-cresyl sulfate may be distinct and may possibly be completely different. This is underscored by the observation that *p*-cresyl sulfate, but not *p*-cresol, has a proinflammatory effect on leukocytes *in vitro*.[53] Both *p*-cresol and *p*-cresyl sulfate promote the shedding of endothelial microparticles by human umbilical vein endothelial cells.[54] These findings undermine the traditional view that sulfate conjugation is merely a detoxification step.

In support of these *in vitro* data, we recently reported that free serum concentrations of *p*-cresol (which include both *p*-cresol and its sulfate conjugate) are independently associated with overall mortality[55] and cardiovascular disease in HD patients.[56]

Protein fermentation metabolites and bone mineral metabolism

Bone metabolism in patients with renal failure is characterized by parathyroid hormone (PTH) resistance. Recent *in vitro* data show that indoxyl sulfate is one of the factors that induce skeletal resistance to PTH. Indoxyl sulfate enters osteoblasts through OAT-3 and induces osteoblast dysfunction, including decreased expression of the PTH receptor (PTHR).[57] Preventing the accumulation of indoxyl sulfate in blood improves bone formation and increases *PTHR* gene expression.[58]

MICROBIAL METABOLISM AND TARGETED THERAPY IN CKD

Presently, uremia can only be treated by renal replacement therapy. Drug therapy has proved to be unsuccessful or, to a large extent, has not been tested.[1] Efforts are mounting to study drug therapy targeted to the colonic microenvironment in CKD. These therapies can be broadly divided into two categories: (1) those that aim to modulate bacterial growth in the colon, leading to reduced generation of bacterial toxins; and (2) those targeting adsorption of toxic end products of microbial fermentation. Both interventions should lower bacterial toxin levels in the host. Because of the inaccessibility of the colon, one has to rely mainly on (serum and urinary) biomarkers to evaluate the efficacy of these interventions.[6,59]

Modulation of the microbiota as a target in CKD

The generation of toxic microbial protein metabolites can be modulated by selectively increasing saccharolytic and reducing proteolytic bacteria in the colon. Both probiotics and prebiotics have been shown to influence the composition of colonic microbiota.

Probiotics have been defined as 'viable organisms that, when ingested in sufficient amounts, exert positive health effects.' The most frequently used strains include *Lactobacillus*, *Streptococcus*, and *Bifidobacterium*.[60] Although numerous studies have evaluated the effects of probiotics, only a limited number have looked at their effects in renal disease (Table 2). Only intermediate end points, for example, change in serum concentrations or urinary excretion of marker molecules, were examined. Studies investigating the impact of probiotics on hard clinical end points (e.g., cardiovascular events, cancer, mortality) in renal disease have not been conducted to date.

The term prebiotic, first coined by Gibson and Roberfroid, refers to 'a nondigestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, and thus improves host health.'[60] Whereas numerous compounds are known to escape digestion in the small intestine, a limited number of molecules result in selective stimulation of microbiota. At present, only bifidogenic, nondigestible oligosaccharides (particularly inulin, its hydrolysis product oligofructose, and (*trans*)galacto-oligosaccharides) fulfill all the criteria for prebiotic classification.[61] In a study of nine patients with CKD but not yet on dialysis, Younes *et al.*[62] found that fermentable carbohydrates shifted nitrogen excretion from the urinary route to fecal excretion, thereby reducing plasma urea concentrations. Whether this resulted in a decreased generation of other URMs was not studied. A study in healthy volunteers has demonstrated lowering of urinary *p*-cresol excretion by the ingestion of a 50/50 v/v mixture of inulin and fructo-oligosaccharides.[59] A recent phase I/II trial confirmed that *p*-cresol generation and *p*-cresyl sulfate serum concentrations were lowered in HD patients by this prebiotic.[63]

Another way to reduce generation of bacterial toxins is to limit or modify the ratio of available CHO to nitrogen, which, as outlined previously, is an important regulator of bacterial α-amino nitrogen metabolism.[27,28] To lower the production of toxic metabolites originating from protein fermentation, it is important to increase the colonic availability of CHO.

To increase CHO intake, one approach is the administration of a prebiotic such as digestion-resistant starches. An alternative method to increase delivery of fermentable CHO to the colon is to inhibit CHO assimilation by means of small intestinal α-glucosidase inhibitors such as acarbose (Glucobay; Bayer Healthcare, Diegem, Belgium). In a pilot study in healthy volunteers, we evaluated the effect of acarbose on the generation and serum concentrations of *p*-cresol. Serum concentrations of *p*-cresol and the 24-h urinary excretion of *p*-cresol, reflecting the colonic generation rate, were significantly lower after acarbose treatment.[64] A randomized controlled trial evaluating the effects of acarbose in patients with CKD not yet on dialysis is ongoing.

A further approach that may also affect the generation of URMs is dietary intervention. Fruit and vegetables are an important source of dietary fibers (i.e., nondigestible CHO). Patel *et al.*[65] demonstrated that a vegetarian diet reduced urinary excretion of indoxyl sulfate and *p*-cresyl sulfate. However, fruit and vegetables are often restricted in CKD because they are rich in potassium. Another dietary modification, limiting protein intake might also reduce URM generation. This too may not be appropriate, as it confers an increased risk of protein energy malnutrition.

Adsorption of microbial metabolites

A second approach to treat uremia, other than reducing toxin generation rates in the colon, is to limit intestinal absorption. This can be achieved by reducing the availability of generated microbial metabolites through adsorption onto high-affinity surfaces. AST-120 (Kremezin; Kureha Chemical Industry, Tokyo, Japan) is an orally administered adsorbent consisting of spherical carbon particles 0.2–0.4 mm in diameter.[66] It is capable of adsorbing significant amounts of various organic compounds in the large intestine, including indoxyl sulfate,[8,47] *p*-cresol,[67] and food-derived advanced glycation end products.[68] It has been shown to retard the progression of renal failure in Japanese patients with mild-to-moderate CKD.[46,69] A phase II dose-finding study in US patients with CKD confirmed a dose-dependent reduction in indoxyl sulfate serum concentrations.[47] A large, multicenter randomized trial is currently testing whether AST-120 can slow the progression of CKD (Evaluating Prevention of Progression In Chronic Kidney Disease (EPPIC-1/2); ClinicalTrials.gov ID, NCT00500682/NCT00501046).

Sevelamer hydrochloride (Renagel; Genzyme, Cambridge, MA, USA), a non-metal-based phosphate binder, is another potentially useful adsorbent therapy. In addition to phosphate binding, it has been shown to bind URMs *in vitro*, including indole (10–15%) and *p*-cresol (40–50%, dependent on pH).[70] Despite this observation, sevelamer did not result in decreased serum concentrations of indoxyl sulfate or *p*-cresol in a mouse model of CKD.[71] Whether treatment with sevelamer in humans alters the serum concentration of microbial metabolites (e.g., indoxyl sulfate or *p*-cresyl sulfate) remains to be investigated.

Colonic transit time as a target in CKD

Currently, drugs that selectively reduce colonic transit times are not available, and it is unlikely that targeted therapies will be developed in the near future. However, several therapies—including prebiotics—also reduce colonic transit times, in addition to other effects. Conversely, treatments that prolong colonic transit might result in increased generation and absorption of URM. The relevance of this phenomenon has not been studied yet.

CONCLUSION

Uremic retention solutes are implicated in the uremic syndrome and might be a missing link to explain the persistently high mortality rates in CKD. An important subgroup of uremic retention solutes originates from bacterial protein metabolism in the large intestine. Several bacterial URMs have been identified that have toxic effects *in vitro* and that may contribute *in vivo* to progression to renal failure and mortality in patients with CKD. Thus, bacterial metabolism and its metabolites are rational therapeutic targets in CKD.

Two main therapeutic avenues exist: (1) interventions that modulate bacterial growth such as probiotics, prebiotics, and dietary modification; and (2) adsorbents that bind bacterial URMs in the intestines to reduce their absorption by the host.

Probiotics and prebiotics have been shown to modify intestinal microbiota and thus provide clinical benefit in healthy individuals, but this has not been fully studied in renal disease. Blocking CHO assimilation in the small intestine through α-glucosidase inhibitors such as acarbose may help modify nutrient availability, which leads to less toxic protein fermentation in the colon of patients with CKD. An ongoing trial in CKD may reveal the utility of this approach. Dietary modification may also offer some benefits in modifying intestinal nutrient availability but is limited by specific dietary considerations in patients with CKD.

Alternatively, adsorbent therapies may offer promise for reducing URM levels in patients with CKD. A multicenter randomized trial is currently testing whether AST-120, an orally administered adsorbent consisting of spherical carbon particles, can slow progression of CKD. An additional promising candidate is sevelamer. It is already in use in dialysis patients to reduce hyperphosphatemia by binding intestinal phosphorus, and may also provide clinical benefits by binding other harmful compounds in the intestines, such as URMs. This potential is currently an active area of interest in patients with CKD.

DISCLOSURE

Dr Evenepoel has been a consultant and a speaker for Genzyme and Amgen. Dr Bammens has been a consultant for Amgen, and a speaker for Baxter. Dr Meijers and Dr Verbeke have nothing to disclose.

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