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The relationship between dietary fiber, microbiota and kidney diseases in cats and dogs

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ABSTRACT

Chronic kidney disease (CKD), which is an increasingly common disease in humans and a global health problem, is also a very common disease in cats and dogs. CKD can be caused by primary glomerulopathies, nephroliths, renal dysplasia, polycystic kidney disease, pyelonephritis, renal carcinomas, nephrotoxic drugs and toxins. The fact that cats diagnosed with CKD and with shorter survival time have low or excess body weights suggests that there may be strong correlations between diet and CKD. In recent years, effects of nutrition on microbiota changes and the role of these changes in diseases have taken particular interest in veterinary medicine. This review article focuses on the curative role of dietary fiber intake, which targets the intestinal microbiota and aims to reverse dysbiotic factors in cats and dogs with chronic kidney disease.

Keywords: dietary fiber, prebiotics, renal diseases, microbiome

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Introduction

The complex relationship between nutrition and the development and prevention of various diseases in cats and dogs is one of the most popular topics in recent years. There is a rising incidence of kidney disease (CKD) in humans and is also quite common in cats and dogs. In a study conducted in the United Kingdom showed that chronic kidney disease was the most common cause of death in cats over 5 years of age, with a rate of 13.6% (O'Neill et al., 2015), and the prevalence of CKD in dogs was reported to vary between 0.5-7% (Lund et al., 1999).

Low and excess body weights were associated with shorter survival rate in cats diagnosed with CKD (Freeman et al., 2016). This correlation suggests that there might be strong connections between diet, and CKD management. On the other hand, the complex relationships between the microbiome and the metabolic and immune systems also play a direct role in the pathogenesis of diseases (Hoffmann et al., 2015). Dietary fibers are partially fermented parts of plants that cannot be digested hydrolytically, and dietary fiber cause effective changes in the microbiota and may indirectly affect morbidity and mortality (Kwon et al., 2022). Although the role of microbiota changes in the pathogenesis, treatment and prevention of diseases in pet medicine is not well understood and many studies today focus on this area. CKD causes significant quantitative and qualitative changes in the intestinal microbiota (Vaziri et al., 2012). Since uremia is one of the most serious complications of kidney diseases, increased urea flow into the intestines causes an increase in lumen pH and pathogenic bacteria, resulting in complications such as the formation of uremic toxins, translocation of endotoxins and the formation of secondary diseases. Uremic toxins hence are used as clinical biomarkers in CKD.

Kidneys are essential for homeostasis and kidney diseases affect many body systems. Kidneys are responsible not only for waste management and acid-

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base regulation, but also for many metabolic functions such as regulation of blood pressure (renin-aldosterone) and endocrine functions (erythropoietin and vitamin D). These interactions make kidneys more susceptible to dietary effects and they are significantly affected by eating habits. Chronic kidney disease is generally defined as a structural and functional disorder in one or both kidneys that lasts longer than 3 months (Bartges, 2012). This definition is similar in both humans and cats and dogs. Since chronic kidney disease is generally common in older animals, it is difficult to establish the differential pathology of mortality. The staging of CKD is described by IRIS (International Renal Interest Society), where stage 1 defines non-azotemic disease and stage 4 defines severe end-stage renal azotemia. Main causes of CKD are primary glomerulopathies, nephroliths, renal dysplasia, polycystic kidney disease, pyelonephritis, renal carcinomas, nephrotoxic drugs and toxins (Chacar et al., 2020). While the primary factor is often unknown, continuous damage to the kidney and infiltration of inflammatory cells creates irreversible inflammation and initiates renal fibrogenesis (Reynolds and Lefebvre, 2013). It has been reported that the source of inflammation in CKD might be the gastrointestinal system (Lau et al., 2015). Renal fibrosis is the most common pathological process in CKD, and so far no drug has been proven to cure fibrosis (Kawabata et al., 2023). CKD is a state of progressive loss, that is, it is characterized by a continuous decrease in kidney functions (Chen et al., 2020).

Plasma/serum creatinine (Scr) and blood urea nitrogen (BUN) concentrations are routinely used to estimate glomerular filtration rate (GFR) or to estimate and diagnose acute-chronic kidney diseases in veterinary clinics. GFR, known as a sensitive indicator of functional kidney, is defined as the volume of ultrafiltrate formed in the nephrons of both kidneys per unit of time (De Loor et al., 2013; Kerl and Cook, 2005). Decrease in glomerular filtration rate and tubular secretion leads to accumulation of nitrogenous waste and indirectly to uremia. The decrease in urea excretion from the kidneys causes an increase in the secretion of urea into the gastrointestinal tract, which is converted into ammonia by urease-produced bacteria (Carvalho et al., 2021). Many metabolic toxins accumulate in kidney diseases, and the most well-known toxins are Scr and BUN among 146 uremic toxins. Scr and BUN levels are affected by hydration and muscle mass. CKD can be detected earlier in cats and dogs with the increase in Symmetric Dimethylarginine (SDMA) levels than with the increase in Scr, thus provide opportunities treating animals when they have adequate nutrition. Diagnosis of the disease in advanced stages also limits survival time.

The gut microbiota is extremely diverse and consists of bacteria, archaea, viruses and eukaryotic organisms. The combined genetic potential of this endogenous flora is called the microbiome (Nicholson et al., 2012). Although bacteria are the most abundant group, it is very difficult to identify all bacteria with current molecular methods. The bacterial population is mostly concentrated in the large intestine. It is estimated that the microbial load in the intestine varies between 1012 and 1014, approximately 10 times higher than the host cells (Suchodolski, 2011). It was reported that the duodenum of cats contains higher numbers of bacteria than that of dogs, with anaerobic bacteria predominating (Johnston et al., 1993).

In recent years, the definition of gastrointestinal functionality has been encountered. Celi et al. (2017) defined gastrointestinal functionality as a stable state in which the microbiome and the intestinal tract are in symbiotic balance and the animal welfare and performance are not restricted due to intestinal dysfunction. The main components of this definition are gastrointestinal barrier and microbiota. According to Souza et al. (2023) higher α-diversity value and higher number of Faecalibacterium, Turicibacter, Blautia and Fusobacterium in dogs are biomarkers of gastrointestinal functionality. The dominant phyla in dogs and cats are Firmicutes (including Clostridia and Bacilli), Fusobacteria, and Bacteroides (Suchodolski, 2022). These are followed by the Proteobacteria and Actinobacteria phyla (Handl et al., 2011; Middelbos et al., 2010). However, the microbiome is dynamic and could change throughout lifetime in response to the environment, diet, stress, age, diseases and medication use. Additinoally, fecal bacterial profile analyses showed that each dog had a unique and relatively stable bacterial profile (Simpson et al., 2002). The disadvantage of fecal microbiome analyzes is that it is unclear what extent they reflect the microbiomes of the intestinal regions. Today, molecular methods targeting the 16S rRNA gene are accepted standard for identifying bacterial microbiota. The diversity of the microbiome is also associated with the host health, and loss of diversity is associated with diseases.

Changes in the diversity or composition of the intestinal microbiota are defined as dysbiosis. Cats suffering from CKD are known to have dysbiosis (Summers et al., 2019). It is currently thought to be only a symptom of diseases and actively contribute to pathologies, since dysbiosis has not yet been proven to be the cause of any disease. While dysbiosis exacerbates inflammation in susceptible individuals, normobiosis restoration is the desired result

(Suchodolski, 2016). Dysbiosis does not always involve pathogens because the absence of important commensals can also be detrimental in the absence of pathogens.

Chronic diseases are closely related to dysbiosis. Recently, many studies have been conducted on whether dysbiosis contributes to the progression of CKD. Wilkins et al. (2019) explained that the most common genera in kidney diseases are Bacteroides, Corynebacterium, Anaerococcus, Prevotella, Rothia, Sutterella, Eubacterium, Fusobacterium, Leptotrichia, Parabacteroides, Peptoniphilus, Porphyromonas, and Veillonella. Hanges in microbiota profile/diversity are closely related to uremic toxin formation levels (Hasegawa et al., 2017). In CKD, gastrointestinal tract environment modifiers such as urea, uric acid, trimethylamine-N-oxide (TMAO), indole, p-crysol, as well as dietary restrictions, slow colonic transit, drugs such as iron-containing compounds, phosphate binders and antibiotics are considered as causes of dysbiosis. (Jazani et al., 2019; Mafra and Fouque, 2015). The overgrowth of bacteria producing urease, indole and crysol-forming enzymes as a result of the flow of urea and other toxins into the gastrointestinal lumen increases the lumen pH and causes the microbiota composition to change. Protein fermentation leads to the formation of uremic toxins that lead to the progression of CKD. Indoxyl sulfate, derived from tryptophan metabolism by the intestinal flora, and p-cresol, produced from the partial breakdown of tyrosine and phenylalanine, are among the most studied uremic toxins (Summers et al., 2019; Wu et al., 2011). Since 90% of the indoxyl sulfate accumulated in the blood is bound to albumin of uremic patients, the main excretion is done through tubular secretion, and accumulation occurs as a result of decreasing urinary excretion as CKD progresses (Hasegawa et al., 2017; Niwa, 2010). Both indoxyl sulfate and p-cresol cause oxidative stress by inducing the production of reactive oxygen species and cause progression of nephrotoxicity (renal fibrosis, glomerular sclerosis) by functioning as nephro-vascular toxins (Dou et al., 2007; Enomoto et al., 2002; Niwa, 2010). It has also been shown that the increase in p-cresol occurs during uremia may contribute to immunosuppression in dogs with CKD by changing neutrophil function in dogs (Bosco et al., 2016). Indoleacetate and TMAO levels are also useful in the diagnosis and staging of CKD in cats (Nealon and Winston, 2023).

It was shown that fermentable fibers or oligosaccharides caused a decrease in blood urea levels (Younes et al., 1995). Furuse et al. (2014) found that addition of galactooligosaccharide (GOS) to the diet of nephrectomized rats significantly reduced cecal indole and serum indoxyl sulfate concentrations and ameliorated tubulointerstitial damage. The decrease in cecal indole level was explained by an increase in indole-negative bacteria (e.g., most species of Bifidobacteriaceae) and a decrease in indole-positive bacteria (e.g., some species of Clostridiaceae). Wang et al. (2020) reported that Eggerthella lenta and Fusobacterium nucleatum increased uremic toxin production in rats with CKD and contributed to the progress of kidney disease, and that probiotic intervention with Bifidobacterium animalis reduced the severity of CKD by decreasing both these species and toxin production (Wang et al., 2020). Souza et al. (2023) in their very recent study, it was reported that cassava fiber produced lower indole, phenol and p-cresol in dogs compared to a control diet containing no fiber. Kieffer et al. (2016) fed rats with CKD high levels of fermentable dietary fiber and they observed a decrease in cecal pH and serum/urine indoxyl sulfate, p-cresol levels and an increase in the Bacteriodetes-Firmucutes ratio. A study in humans also reported a decrease in p-cresol levels after consumption of yoghurt containing Lactobacillus and Bifidobacterium animalis species (Stuivenberg et al., 2023). Hall et al. (2020) showed that the diet containing soluble fiber (scFos) led to lower phenolic uremic toxin production compared to the diet containing insoluble (apple puree) fiber when consume similar total fiber ratios but a two fold difference in soluble fiber to CKD stage 1 and stage 2 cats. Ephraim and Jewell (2020) compared feeding high and low soluble fiber diets in dogs with CKD over a 10-week period, they showed that the high soluble fiber diet was more successful in reducing uremic toxins.

Inflammation is a mediator and common feature of the progression of chronic kidney disease and its complications (Vaziri et al., 2012). The main trigger of inflammation is the gastrointestinal system (Lau et al., 2015). Vaziri et al. (2012) showed that tight junctions were disrupted as a result of serious decreases in occludin, claudin-1 and ZO-1 protein expressions in the colonic mucosa of nephrectomized rats, and they also proved that that condition contributed to systemic inflammation with progression in CKD. Enterocytes and paneth cells regulate luminal bacteria by producing mucus and antibacterial factors in the intestine (Pelaseyed et al., 2014). When deprived of fiber, commensal bacteria damaged the intestinal protective mucus layer, paving the way for pathogen invasion (Desai et al., 2016). This situation also explains conditions such as increased intestinal permeability, systemic inflammation and microbial flora-induced endotoxemia associated with the uremic

result of high permeability, translocation of bacteria, bacterial products and toxins, a different blood microbiome profile is observed in patients with CKD compared to healthy individuals. Shah et al. (2019) performed a quantitative analysis of the blood microbiome in CKD patients for the first time and found a decrease in α diversity and an increase in the Proteobacteria phylum, Gammaproteobacteria class, Enterobacteriaceae and Pseudomonadaceae families, although β diversity was similar compared to healthy controls. Additionally, this study showed that progression in CKD or decline in GFR rate also leads to increases in the Proteobacteria phylum.

Dietary Fiber and CKD

Dietary fiber, first defined by Hipsley in 1953, is defined by AAFCO (Association of American Feed Control Officials) as the partially fermented components of feedstuffs that cannot be digested hydrolytically (Fahey et al., 2019; Hipsley, 1953). All currently known prebiotics are carbohydrates, and many different carbohydrate derivatives are marketed as prebiotics in worldwide (Ranganathan, 2018). While all prebiotics can be classified as fiber, not all fibers are prebiotic and prebiotic fibers provide effective changes in the microbiome (Brownawell et al., 2012). Short-chain fatty acids (SCFA) are formed as a result of the fermentation of dietary fibers by the microbiota. The most abundant of these carboxylic acids, which contain one to six carbon atoms, is acetate, followed by propionate and butyrate (Wong et al., 2006). Alexander et al. (2018). Compared the dietary intake of a non-prebiotic fiber product (cellulose) and a prebiotic (inulin) product and found that the latter fiber product caused higher increases in fecal short-chain fatty acids (SCFA), an increase in Firmicutes and a decrease in Proteobacters. Dietary fiber supplementation can affect bacterial populations by providing additional energy in the colon, and generally Lactobacillus and Bifidobacterium and butyrate-producing bacterial groups increase (Kafeshani, 2017; Simpson et al., 2002). Most fibers act by enriching fiber-fermenting SCFA-producing Firmicutes (Pilla and Suchodolski, 2021). Enterocytes and colonocytes provide 60-70% of their energy from SCFA oxidation (Jazani et al., 2019). Kawabata et al. (2023) suggested that SCFAs enter the bloodstream via monocarboxylate carriers and are absorbed and used by the kidney via the G-protein coupled receptor. They also reported that acetate reduces the production of reactive oxygen species by increasing the viability of human proximal tubule epithelial cells under oxidative stress.

The intestinal microbiota is sensitive to nutrients, and diet is the main regulator of its activity (Nicholson et al., 2012). While sharp changes in macronutrients are necessary for changes in bacterial taxa and bacterial metabolites, micronutrients change the microbiota function (Pilla and Suchodolski, 2021). David et al. (2014) showed that only 5 days of consumption of diets consisting entirely of animal or plant products caused effective changes in the microbial population and showed rapid adaptation of the microbiota.

The most studied dietary fibers today are inulin, lactulose, mannan-oligosaccharides (MOS), fructo-oligosaccharides (FOS) and galacto-oligosaccharides (GOS). It is known that the genera responsible for metabolizing oligosaccharides are Lactobacilli and Bifidobacteria (Perini et al., 2023). It is thought that the fermentation of inulin-type fructans, which are rapidly fermented in the colon for SCFA production, in the large intestine occurs preferentially with Bifidobacterium (Roberfroid, 2005). It is known that there are decreases in Bifidobacaterium and Lactobacillus genera in CKD (Crespo-Salgado et al., 2016). Those studies also showed that dose-dependent effects of both FOS and inulin. Bifidobacteria are among the first to colonize the neonatal intestine, they play an important role in modulating both the metabolic and immune activities of the host. Inulin supplementation at a dose of 50 mg/kg for 21 days in British Shorthair cats resulted in increased Firmicutes and Actinomycetes, while Bacteroides and Proteus numbers decreased (Liang et al., 2023). Garcia-Mazcorro et al. (2017) reported that consumption of prebiotic mixtures of FOS and inulin up to 31 mg/kg did not significantly alter the abundance of most bacterial groups in the feces of healthy dogs. Most studies using FOS at concentrations of 1% or 2% on a dry matter basis showed no effects on important gastrointestinal variables such as SCFA, BCFA, fecal ammonia, fecal pH, fecal score, and fecal microbial population (Perini et al., 2023). In a meta-analysis study evaluating the use of prebiotics in dogs, it was stated that many prebiotic additives such as FOS, MOS, and inulin at 1.4% of the diet on a dry matter basis increased the number of Bifidobacterium and Lactobacilli species in the feces and this increase was correlated with the dose (Patra, 2011). Addition of FOS to the diet of Beagle dogs for 8 weeks increased the number of Bifidobacterium and Bacteroides species, while Clostridium perfringens decreased below the detection level after a 4-week period (Ide et al., 2020).

Restriction of fruits, vegetables and high-fiber foods is recommended for CKD patients to prevent excessive intake of potassium. Food intake surveys in human hemodialysis patients showed significantly

reduced intake of dietary fiber, an important source of fermentable carbohydrates, and substances such as potassium and vitamin C (Yang et al., 2018). This facilitates the transition from saccharolytic to proteolytic metabolism. Shortage of complex carbohydrates, required for the saccharolytic microbiota, may lead to a decrease in SCFA production and, as a result, a deficiency of nutrients required for colonocytes and Treg cells (Jazani et al., 2019). Bifidobacterium, Lactobacillus and Faecalibacterium are of high importance due to their in carbohydrate fermentation resulting in butyrate, which is the energy source for colonocytes (Turroni et al., 2011). Toxic end products were accumulated with increased metabolism of protein and other nitrogenous compounds as a result of lack of carbohydrate sources or high protein/carbohydrate ratio (Jazani et al., 2019; Montemurno et al., 2014). Proteolytic catabolism is leaded to higher ammonia concentration in the gastrointestinal tract, resulting in a shift to alkaline pH and an increase in proteolytic species. Imbalance in favour of proteolytic species will have a fundamental role in the progression of CKD as it will increase uremic toxin production (Yang et al., 2018).

Microbiota and CKD

Removal of toxins such as urea, uric acid, creatinine, indole and phenols originating from the intestine using probiotics/prebiotics is called enteric dialysis (Prajapati et al., 2023). Nakabayashi et al. (2011) supplemented a synbiotic enriched with galactoolisaccharides to nine hemodialysis patients for two weeks and they observed a significant decrease in serum p-cresol levels but indoxyl sulfate and phenol levels were not affected.

While the amount of uremic toxin increases with constipation in people with CKD, only one study examined the relationship between CKD and constipation in cats and dogs. While 42% of cats with CKD had a defecation frequency of once a day or less, no difference for stool scores was observed between healthy cats and cats with CKD (Jones et al., 2022). Incubation with indoxyl sulfate and p-cresol sulfate in mice with CKD creates an abnormal contraction pattern in the intestines and doubles the gastrointestinal transit time (Hoibian et al., 2018). As CKD progresses, protein assimilation also deteriorates. Summers et al. (2020) found higher concentrations of fecal isovaleric acid correlated with p-cresol in 28 cats with CKD and concluded that this was evidence of protein malassimilation. Higher protein flow to the colon as a result of malassimilation supports the decrease of Bifidobacterium, which is a saccharolytic bacteria with high ability to ferment dietary fibers, and the proliferation of proteolytic bacteria (Summers et al., 2023). Prolonging the colonic transit time also reduces the amount of SCFA producing from carbohydrates entering the colon (Yang et al., 2018). Another effect of SCFAs is that they support regulate intestinal motility (Smith et al., 2013). SCFAs are both a direct energy source and signalling molecules that affect intestinal transit time through receptors (GPR41) on enteroendocrine cells (Samuel et al., 2008).

Similar pathways occur in the pathogenesis of multiple non-communicable diseases. Studies conducted in humans have shown that multimorbidity, that is, having two or more chronic conditions at the same time, is no longer an exception (Pietzner et al., 2021). Heart failure (HF) is often accompanied by CKD, and a 2-3 fold increase in heart rate is reported in patients (Hua et al., 2023). Sympathetic hyperactivity in CKD is observed even in the early stages (Kiuchi et al., 2020). When renal blood flow decreases, the renin-angiotensin-aldosterone(RAAS) system is activated. Angiotensin II release, which first aims to increase the GFR rate by narrowing the efferent arteriole, is a response to nephron loss, but incompatibilities in this response result in proteinuria and cause the development of hypertension (Lawson and Jepson, 2021). The kidneys are seriously affected by hypertensive damage. Hypertension due to the RAAS system cannot be created in germ-free mice (Karbach et al., 2016). It is also known that germ-free mice have lower blood pressure than conventional mice (Moghadamrad et al., 2015). Decreased diversity in the microbiota and changes in enterotype distribution are associated with both prehypertension and hypertension (Li et al., 2017). Liu et al. (2022) demonstrated for the first time the presence of live bacteria in the kidneys of hypertensive and normotensive (pre-hypertensive/spontaneous hypertensive) rats and reported that dysbiosis in the kidney microbiota was the cause of hypertension rather than its consequence. This study predicted that the source of these bacteria in the kidneys was the gastrointestinal tract. Addition of Tatar buckwheat, which has prebiotic/probiotic properties, to the diet affected the intestinal microbiota, reduced bacterial transport to the kidneys, and reduced blood pressure through the reorganization of the core microbiota in the kidneys.

Although both soluble and insoluble fibers have been shown to bind to minerals and inhibit absorption, properties that enhance mineral absorption have also been demonstrated for soluble fibers (Baye et al., 2017). Fiber is fermented in the colon and make the minerals ready for absorption (Metzler and Mosenthin, 2008). As a different way, the colon pH decreases with the formation of volatile fatty acids as

dietary fiber fermentation and lead to increase the solubility of phosphorus and ensure its absorption (Lopez et al., 2000). Varley et al. (2010) did not observe any changes in gastrointestinal pH by adding inulin to the diets of pigs and phosphorus and calcium utilization were not affected. In laboratory animals, dietary supplements containing acacia fiber were found to increase femur calcium, magnesium, phosphorus and zinc concentrations, whereas inulin supplementation did not have such an effect (Massot-Cladera et al., 2020). These conflicting results in both studies can be attributed to the use of low amounts of inulin addition to the diets. Because, Rideout and Fan (2004) showed reduced urinary P loss in pigs after addition of 50 g/kg inulin. Supplementation of different amounts of dietary FOS in healthy dogs increased the apparent total channel digestibility (ATTD) of calcium, magnesium, sodium, zinc, and iron compared to a diet without FOS (Pinna et al., 2018). In CKD, this mineral-fiber interaction becomes even more complex.

The use of fermentable fibers raises concerns about limiting the effectiveness of phosphorus-binding drugs because these drugs used in CKD allow higher amounts of dietary phosphorus to reach the colon. A thesis study conducted in human hemodialysis patients showed that inulin supplementation did not reduce fecal phosphorus excretion compared to the control group (Biruete, 2017). Very recently, Biruete et al. (2023) showed that fermentable dietary fibers increase circulating levels of Fibroblast Growth Factor-23 (FGF), thus affecting phosphorus homeostasis by reducing blood phosphorus levels. Hyperphosphotemia is a natural stimulant for FGF-23 and is aimed at correcting abnormal serum phosphate concentration. Recently, a high correlation between indoxyyl sulfate, phosphate, and FGF-23 has been demonstrated in cats (Liao et al., 2019). Additionally, in latter study, when indoxyl sulfate was controlled, the correlation between FGF-23 and phosphate became insignificant, whereas when FGF-23 was controlled, the relationship between indoxyl sulfate and phosphate remained significantly important. While the most important sources of phosphate in the diet are high protein ingredients and feed additives, there are huge difference between the two sources on their usability. While inorganic phosphates in additives are absorbed at rates more than 90%, 70-80% of the phosphates in animal proteins and only 50% of those in vegetables (Favero et al., 2021). Therefore, dietary change is essential to restrict phosphate absorption.

Dietary fibers should not be used as the sole tool in the management of kidney diseases. In special diets used for kidney diseases in cats and dogs, the protein, phosphorus and sodium content is reduced, while the calorie density and levels of potassium, B vitamins, antioxidants and ω-3 polyunsaturated fatty acids (PUFA) are increased (Machado et al., 2022). Diet modification studies in humans have been conducted in different groups. Results showed that the risk of death was higher in the very low protein (0.28 g/kg/day) intake in group of non-diabetic chronic kidney disease stage four people (Menon et al., 2009). Low-protein diets aim to correct metabolic acidosis, the most common complication of CKD, by reducing net endogenous acid production and potential renal acid load (Di Iorio et al., 2017). However, controlling daily intake and avoiding malnutrition is important. Hall et al. (2016) stated that a diet enriched with high-quality protein sources, like fish oil, antioxidants, L-carnitine, controlled sodium concentration, and fiber-rich fruits and vegetables was more likely to improve renal function in dogs with high serum SDMA but not azotemic.

Conclusion

The most important source of uremic toxins produced by the intestinal microbiota is diet, and reducing the source and amount of uremic toxins in CKD is the therapeutic goal. Indoxyl sulfate, p-cresol sulfate, and trimethylamine-N-oxide are the most studied uremic toxins in both humans and animals. Since our current knowledge shows a linear correlation between these toxins and CKD severity, it is very important to try to utilize the benefits of dietary fibers in disease management. Prebiotic dietary fibers might be highly beneficial agents in achieving this goal.

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