NUTRITIONAL MANAGEMENT OF RENAL DISEASE

An Evidence-Based Approach

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Today's Veterinary Practice is delighted to announce that the **American College of Veterinary Nutrition** (**acvn.org**) has partnered with *TVP* to bring our readers the **NUTRITION NOTES** column.

The primary objectives of the ACVN are to:

- Advance the specialty area of veterinary nutrition
- Increase the competence of those practicing in this field
- Establish requirements for certification in veterinary nutrition
- Encourage continuing education for both specialists and general practitioners
- Promote evidence-based research
- Enhance dissemination of the latest veterinary nutrition knowledge.

The ACVN achieves these objectives in many ways, including designating specialists in animal nutrition, providing continuing education through several media, supporting veterinary nutrition residency programs, and offering a wide array of resources related to veterinary nutrition.

By bringing this column to *TVP* readers, the ACVN is reaching out to all veterinary professionals to provide the highest quality, cutting edge information on companion animal nutrition, contributed by their foremost nutrition specialists.

Chronic kidney disease (CKD) is the most common type of renal disease in senior patients, but can occur in animals of all ages. Estimated incidence of CKD in all dogs and cats is 0.5% to 1.5%, respectively, and, in cats over 15 years of age, 30%.[1] In senior patients, CKD commonly results in morbidity and mortality.[2]

CKD is defined as *the presence of structural or functional abnormalities of one or both kidneys that have been present for an extended period of time, usually 3 months or longer*. It is characterized by irreversible and progressive loss of kidney function, leading to azotemia, uremia, and clinical signs associated with diminishing renal function.

A **uremic crisis** is defined as a patient having at least 2 of the following clinical signs: depression, lethargy, anorexia, vomiting, ammonia breath odor, or uremic stomatitis.

Successful treatment of CKD requires a multi-modal approach, which involves identifying and eliminating exacerbating factors, combined with appropriate dietary and medical management.[3-5]

EVIDENCE-BASED THERAPIES

Many therapeutic interventions have been developed or advocated for management of CKD; however, evidence of efficacy or effectiveness of these interventions is often lacking or highly variable. If current recommendations undergo the scrutiny of evidence-based medicine, very few meet the criteria to receive a Grade I designation (**Table 1**, page 52).

Table 1. Quality of Evidence Grading Guidelines[3]

GRADE	EVIDENCE OBTAINED FROM:
Grade I	One or more properly designed, randomized, controlled clinical studies performed in clinical patients of the target species
Grade II	Properly designed, randomized, controlled studies performed using animals of the target species with spontaneous disease in a laboratory or research animal colony setting
Grade III	• Appropriately controlled studies without randomization • Appropriately designed cohort or case-control studies • Studies using acceptable models of disease or simulations in target species • Dramatic results from uncontrolled studies or case series
Grade IV	• Studies conducted in other species • Reports of expert committees • Descriptive studies, case reports, or pathophysiological justification • Opinions of respected experts developed on basis of their clinical experience

Dietary management of CKD is one of the few current recommendations for management of CKD in dogs and cats that has Grade I evidence.[4-9] As a result, dietary management remains the cornerstone of therapy for CKD.

COMPARISON OF DIETARY THERAPIES

Research has shown that, for managing CKD in dogs and cats, veterinary therapeutic renal diets are superior to maintenance diets (**Table 2**).[4,6-9]

Although these studies in both dogs and cats demonstrate that feeding a therapeutic renal diet to patients with CKD is superior to feeding a maintenance diet, the diets in these studies varied in many of the key nutrients for management of CKD, including dietary protein, phosphorus, and fatty acid composition. Therefore, it is unknown which component(s) of the therapeutic renal diets resulted in the benefits observed in these studies.

KEY NUTRIENTS IN DIETARY MANAGEMENT

Commercial therapeutic renal diets vary in their nutritional composition; turn to page 53 for tables detailing the nutritional composition of these diets.

In the cats in Study 4 (**Table 2**), median survival time was longest in cats fed the diet with the highest eicosapentaenoic acid (EPA) content and one of the highest potassium levels. Survival times were lowest for the diet *not* supplemented with EPA and the lowest potassium content.[8] Unfortunately, the identity of the therapeutic renal diets evaluated in this study was not provided, and it is likely that diet composition has changed since this study was published.

The majority of work performed to determine which nutrients are beneficial at what levels in the management of

Table 2. Studies Comparing Veterinary Therapeutic Renal Diets to Maintenance Diets

Study 1. Double-blinded, randomized, controlled study[4] (2002)	
Purpose	**Dogs with spontaneous CKD:** Evaluate whether a therapeutic renal diet or standard maintenance diet was more beneficial
Results	On average, dogs consuming the maintenance diet (*n* = 21) developed a uremic crisis in 252 days; those consuming the veterinary therapeutic renal diet (*n* = 17) did not experience a uremic crisis until 615 days
	Dogs consuming the veterinary therapeutic renal diet had a lower mortality rate.
Study 2. Retrospective clinical study[6] (2011)	
Purpose	**Dogs with CKD:** Determine whether there was an association between body condition score and survival
Results	The observation was made that dogs fed a veterinary therapeutic diet survived significantly longer than those consuming other types of diets (P = 0.03)
Study 3. Prospective diet study[7] (2006)	
Purpose	**Cats with naturally occurring CKD:** Follow cats consuming a therapeutic renal diet and those consuming a maintenance diet for 24 months and compare results
Results	None of the cats that consumed the therapeutic renal diet (*n* = 22) developed a uremic episode, whereas 6 (26%) of those that consumed the maintenance diet (*n* = 23) developed this diagnosis
	Cats consuming the therapeutic renal diet were not euthanized due to progression of CKD, whereas 5 of the cats in the maintenance diet group were euthanized
Study 4. Retrospective study[8] (2005)	
Purpose	**Cats with naturally occurring CKD:** Compare results of feeding 7 commercial therapeutic renal diets versus a conventional diet
Results	Median survival time for cats consuming the conventional diet (*n* = 175) was 7 months; median survival time for those consuming a therapeutic renal diet (*n* = 146) was 23 months
Study 5. Prospective study[9] (2000)	
Purpose	**Cats with CKD:** Compare results of feeding a veterinary therapeutic renal diet versus a maintenance diet
Results	Cats consuming the veterinary therapeutic renal diet survived longer than those consuming the maintenance diet (median survival time, 633 and 264 days, respectively)

Therapeutic Dry Renal Diets for Dogs

Nutrient	Hill's k/d		Iams Renal Plus		Purina NF		Royal Canin Renal LP Modified		Royal Canin Renal MP Modified	
	% DM	g/100 kcal	% DM	g/100 kcal	% DM	g/100 kcal	% DM	g/100 kcal	% DM	g/100 kcal
Protein	14.3	3.3	21.1	5.47	15.89	3.61	NA	3.28	NA	3.9
Phosphorus	0.25	0.057	0.5	0.12	0.29	0.07	NA	0.08	NA	0.1
Fat	19.5	4.5	13.2	3.44	15.67	3.56	NA	3.68	NA	3.77
Total n-3 FA	1.54	0.353	0.58	0.147	0.30	NA	NA	0.168	NA	0.166
Source of n-3 FA	Flaxseed		Fish oil		Fish oil		Fish oil		Fish oil	
Antioxidants	Vitamins C, E, β-carotene		Vitamins A, E, β-carotene		Vitamins A, E		Vitamins A, C, E		Vitamins A, C, E	
Prebiotic Fiber	Beet pulp		Beet pulp, FOS, gum arabic		None		FOS		FOS	

Therapeutic Canned Renal Diets for Dogs

Nutrient	Hill's k/d		NA		Purina NF		Royal Canin Renal LP Modified		Royal Canin Renal MP Modified	
	% DM	g/100 kcal			% DM	g/100 kcal	% DM	g/100 kcal	% DM	g/100 kcal
Protein	14.8	3.2			20.35	4.16	NA	3.67	NA	4.60
Phosphorus	0.22	0.048			0.28	0.06	NA	0.06	NA	0.06
Fat	26.7	5.8			26.63	5.44	NA	5.59	NA	6.51
Total n-3 FA	1.93	0.420			0.56	NA	NA	0.303	NA	0.255
Source of n-3 FA	Flaxseed				Fish oil		Fish oil		Fish oil	
Antioxidants	Vitamins C, E, β-carotene				Vitamins A, E		Vitamines C, E		Vitamins C, E	
Prebiotic Fiber	None				Carrageenan		Guar gum, beet pulp, carrageenan, FOS		Beet pulp, carrageenan, FOS, guar gum	

Therapeutic Dry Renal Diets for Cats

Nutrient	Hill's k/d		Iams Renal Plus		Purina NF		Royal Canin Renal LP Modified-Chicken		Royal Canin Renal LP Modified-Pork	
	% DM	g/100 kcal	% DM	g/100 kcal	% DM	g/100 kcal	% DM	g/100 kcal	% DM	g/100 kcal
Protein	27.9	6.6	32.01	7.12	30.78	7.24	NA	5.66	NA	6.19
Phosphorus	0.49	0.114	0.42	0.093	0.41	0.10	NA	0.12	NA	0.08
Potassium	0.76	0.178	0.64	0.142	0.88	0.21	NA	0.24	NA	0.22
Fat	21.9	5.2	25.48	5.67	12.83	3.02	NA	4.28	NA	5.12
Total n-3 FA	0.26	0.061	0.88	0.190	NA	NA	NA	0.174	NA	0.188
Source of n-3 FA	Fish meal		Fish oil		Fish oil		Fish oil		Fish oil	
Antioxidants	Vitamins A, C, E, β-carotene		Vitamins A, E		Vitamins A, E		Vitamins A, E		Vitamins A, E	
Prebiotic Fiber	Beet pulp		Beet pulp, gum arabic, FOS		None		Chicory pulp, FOS		Chicory pulp, FOS	

Therapeutic Canned Renal Diets for Cats

Nutrient	Hill's k/d		Iams Renal Plus		Purina NF		Royal Canin Renal LP Modified		Royal Canin Renal LP Modified-Morsels in Gravy	
	% DM	g/100 kcal	% DM	g/100 kcal	% DM	g/100 kcal	% DM	g/100 kcal	% DM	g/100 kcal
Protein	28.9	6.5	32.7	7.12	34.69	7.72	NA	5.52	NA	5.57
Phosphorus	0.38	0.085	0.58	0.128	0.49	0.11	NA	0.08	NA	0.09
Potassium	1.18	0.264	0.99	0.217	0.82	0.18	NA	0.20	NA	0.21
Fat	27.0	6.1	22.96	5.07	25.25	5.62	NA	7.05	NA	7.03
Total n-3 FA	0.72	0.162	1.49	0.332	NA	NA	NA	0.383	NA	0.428
Source of n-3 FA	Fish oil		Fish oil		None		Fish oil		Fish oil	
Antioxidants	Vitamins C, E, β-carotene		Vitamins A, E		Vitamins A, E		Vitamins C, E		Vitamins C, E	
Prebiotic Fiber	Psyllium seed husk, guar gum		Beet pulp, gum arabic, FOS		Guar gum, carrageenan		Guar gum, carrageenan, FOS		Guar gum	

caloric basis = nutrient intake for every kcal consumed; DM = dry matter (nutrient content in product after moisture is removed); FA = fatty acid; FOS = fructooligosaccharides; g/100 kcal = as fed; NA = not available; n-3 = omega

CKD has been done in dogs. The remainder of this article will focus on research results from these studies.

Phosphorus

A study was conducted in dogs to determine the effects of high (H) and low (L) levels of dietary phosphorus and protein on renal function and survival in adult dogs with induced CKD.[10]

- Four diet groups (n = 12/group) were fed one of 4 experimental diets for 24 months after surgical reduction of renal mass.
- The experimental diets (**Table 3**, Page 54) contained varying levels of protein and phosphorus listed on a percent dry matter basis (DMB). Diet 4 was most consistent with many veterinary therapeutic renal diets.
- Results showed that:
  - » When renal function was reduced to the point that moderate azotemia (serum creatinine, 3–4 mg/dL) occurred, dietary phosphorus restriction was associated with a longer period of stable glomerular filtration rate (GFR) and improved survival.
  - » Dogs fed high dietary protein had no functional or morphologic evidence of adverse effects compared with dogs fed low dietary protein.

Therefore, this study showed that survival of dogs with induced CKD was enhanced by phosphorus restriction but not by protein restriction.

Table 3. Protein & Phosphorus Levels of Experimental Diets[10]

DIET	PROTEIN	PHOSPHORUS	RATIO
Diet 1	32%	1.4%	H protein : H phosphorus
Diet 2	32%	0.4%	H protein : L phosphorus
Diet 3	16%	1.4%	L protein : H phosphorus
Diet 4	16%	0.4%	L protein : L phosphorus

Omega-3 Polyunsaturated Fatty Acids

Dogs lack the ability to synthesize omega-6 and omega-3 polyunsaturated fatty acids (PUFAs); therefore, they are considered dietary essential fatty acids.[11]

- Dogs require linoleic acid (LA), an omega-6 PUFA, and have the enzyme capability to convert linoleic acid into arachidonic acid (AA), another omega-6 PUFA.
- However, dogs are unable to convert omega-6 PUFAs into omega-3 PUFAs.

Not all omega-3 PUFAs are metabolically equivalent:

- Plant-based sources of omega-3 PUFAs, such as flaxseed, linseed, and canola oil, are rich in alpha-linolenic acid (ALA).
- Marine algae and oily cold water fish are good sources of EPA and docosahexaenoic acid (DHA).

Conversion Rates. While LA is readily converted to AA, ALA converts to EPA and DHA much more slowly. This conversion rate is < 10% in humans, and believed to be rather limited in dogs as well.[12]

Omega-3 PUFA Benefits. While dietary ALA has some benefits in healthy dogs and management of some dermatologic diseases,[13] the majority of therapeutic benefits from omega-3 fatty acids result from:

- EPA: Anti-inflammatory and prostaglandin effects
- DHA: Central nervous system development and retinol function, which are critical during pregnancy and early life.

These omega-3 PUFAs are used in dietary management of kidney disease, cardiovascular disease, idiopathic hyperlipidemia, inflammatory and immune diseases, and osteoarthritis.[11-13]

Therefore, when using omega-3 PUFAs for dietary management of medical conditions, the source should also already contain EPA and DHA because the conversion rate of ALA to EPA and DHA may be too slow to benefit the patient.

Additional Benefits. When nephrons are destroyed in CKD, the remaining viable nephrons hypertrophy in an attempt to compensate, resulting in a maladaptive increase in glomerular capillary pressure (GCP). Dietary omega-3 fatty acid supplementation in the form of fish oil can have beneficial effects in reducing GCP.

In studies by Brown, et al,[14-16] the effects of various dietary omega-6:omega-3 ratios on glomerular hypertension in a canine remnant kidney model were evaluated.

- Three groups of 6 dogs were fed diets with omega-6:omega-3 ratios of 50:1, 25:1, and 5:1 for 10 weeks.
- Omega-3 PUFA supplementation was supplied in the form of fish oil, which is rich in EPA and DHA.
- Results showed the omega-6:omega-3 diet with the 5:1 ratio normalized GCP in dogs with reduced kidney function to a level consistent with that found in dogs with normal kidney function.

Antioxidants

A free radical is any atom or molecule that has a single unpaired electron. Normal aerobic metabolism, along with many environmental factors, contributes to the formation of reactive oxygen species (ROS) in the body. ROS can damage membrane lipids, nucleic acids, and proteins in the body that, in turn, contribute to disease processes.

Oxidative Stress. Normally, antioxidant defense mechanisms adequately remove ROS as they are formed; however, these mechanisms become inadequate as animals age, and progressive oxidative damage is a consistent feature of aging unless adequate dietary sources of antioxidants are provided. Keep in mind, though, that oversupplementation of dietary antioxidants may be as detrimental as deficiency of dietary antioxidants.

Since CKD occurs most commonly in older dogs:

- Oxidative stress can be a contributing factor to the decline in GFR associated with CKD.
- Renal oxidative stress is a problem because surviving hypertrophied nephrons become adaptively hyperfunctional, leading to a dramatic increase in cellular oxidative phosphorylation.[16]

Optimum Supplementation. In a study by Brown,[16] the effects of omega-3 fatty acid and antioxidant supplementation were evaluated separately and in combination in 6- to 8-year-old beagle dogs with induced CKD. Four groups of 8 dogs were fed one of 4 diets (**Table 4**).

The results demonstrated that veterinary therapeutic renal diets supplemented with omega-3 PUFAs from fish oil in combination with antioxidants appear to better slow progression of CKD than diets supplemented with only one or the other or none at all.

Protein

The traditional approach to dietary management of CKD in dogs was reduction of protein intake to less than the minimum levels for adult maintenance (18% DMB) recommended by the Association of American Feed Control Officials (AAFCO). The rationale for this approach consid-

Table 4. Results of PUFA & Antioxidant Supplementation[16]

DIET	PUFA	ANTIOXIDANTS	RESULTS
Diet 1	High omega-3	None	Slowed rate of decline in GFR
Diet 2	High omega-3	Yes	Effects on slowed rate of decline in GFR were additive and statistically significant*
Diet 3	High omega-6	None	Control diet
Diet 4	High omega-6	Yes	Slowed rate of decline in GFR*

- Omega-3 PUFAs from fish oil; omega-6 PUFAs from vegetable oil
- Antioxidants consisted of vitamin E, carotenoids, and lutein

* *Antioxidants also reduced magnitude of proteinuria, glomerulosclerosis, & interstitial fibrosis*

Table 5. Results of High Protein *versus* Low Protein Diet[21]

DIET	LEAN BODY MASS	BODY FAT	RESULTS
16.5% Protein	71.1%	24.8%	Lean body mass (%) was directionally higher and body fat (%) directionally lower with the higher protein diet.
45.6% Protein	76.2%	19.6%	

ered that:

- Reduced protein diets decrease production of nitrogenous waste products excreted by the kidneys
- Protein is one of the major contributors to phosphorus in the diet; reduction of dietary protein also reduces dietary phosphorus levels, which has shown benefit in management of CKD in dogs.[10]

Amount of Dietary Protein. However, reduced dietary protein for management of CKD in dogs is not necessarily beneficial.

1. Senior dogs are less efficient at metabolizing dietary protein than younger dogs and, thus, require more dietary protein to maintain protein reserves and maximize protein turnover rates.[17,18]
2. In humans, loss of lean body mass often accompanies dietary protein restriction, and can result in loss of physical strength, motor coordination, and impaired immune function.[19,20]
3. Loss of lean body mass has also been associated with increased rates of morbidity and mortality in humans, and a similar result was observed in a study in dogs (see **Table 5**).[21]
4. Work by Finco and Brown[10] demonstrated that dietary phosphorus restriction, but not dietary protein restriction, was beneficial in dogs with CKD.
5. In a study by Kealy,[21] 26 healthy pointers, ages 7 to 9 years, were fed a 16.5% or 45.6% protein diet for 2 years. The results of the study are outlined in **Table 5**.

Recently, it has been shown that dietary protein levels can be increased in dogs with CKD without adversely affecting life expectancy. However, the diet must be phosphorus restricted, using protein sources naturally lower in phosphorus concentration, such as soy isolate.[5]

Enteric Dialysis. In addition, by using nonrenal methods of excreting urea from the body, such as enteric dialysis, it may be possible to increase dietary protein fed to dogs with CKD without increasing nitrogen excretion burden on the kidneys. To promote enteric dialysis, diets can be supplemented with certain types of fermentable fiber, such as beet pulp, fructooligosaccharide (FOS), and gum arabic.

A study evaluated 12 healthy adult dogs that, for 14 days, were fed either a normal maintenance diet or the same diet supplemented with a fermentable fiber blend, which included beet pulp, FOS, and gum arabic.[22] Dogs fed the diet containing the fermentable fiber blend had increased fecal nitrogen excretion (34% increase; $p < 0.05$) and decreased urinary nitrogen excretion. Therefore, it appears the body increased nitrogenous waste product excretion via a nonrenal mechanism; this mechanism could be used to potentially increase dietary protein intake in dogs with CKD, without increasing buildup of uremic toxins.

IN SUMMARY

The mainstay of therapy for CKD—in both dogs and cats—is dietary management. Research has shown that:

- Veterinary therapeutic renal diets are superior to conventional maintenance diets for management of CKD.
- Diets containing omega-3 PUFAs in the form of fish oil and rich in EPA are beneficial for both dogs and cats.
- Renal diets supplemented with appropriate amounts

Encouraging Patients with CKD to Eat

Patients with CKD may be reluctant to eat, or may develop food aversions to a diet they currently are consuming. Some proactive steps can help encourage food intake:

1. **Wait to begin a new therapeutic renal diet** until a newly diagnosed patient is no longer anorexic or vomiting. Uremic patients are prone to developing food aversions rapidly, which contraindicates introducing a diet for the patient to consume long-term at that time.
2. **Prevent uremic gastritis**, which can become evident in patients with CKD as the disease progresses. It is often not addressed until the patient becomes symptomatic (vomiting or anorexic), which may result in food aversion. While no studies identify when in the course of disease to consider treatment, an H2 receptor antagonist (ranitidine or famotidine) is recommended in any patient with a serum creatinine level of > 3 mg/dL.
3. **Try a different diet** if a patient refuses the one offered. A number of different commercial therapeutic renal diets are available, and some patients find one diet more palatable than another.
4. **"It is better to eat some of the wrong diet then none of the right diet."** Therapeutic diets are not beneficial if patients refuse to eat them, and the patient's wellbeing is jeopardized when it is not consuming food. Certain ingredients can help enhance a therapeutic diet's palatability.
   - **Dogs:** Tablespoon of mashed potato gravy (works especially well for dry kibble), low-sodium canned green beans, or rice cakes
   - **Cats:** Tablespoon of canned tuna, baby food, or a palatable commercial maintenance diet
   - **Cats:** Mixing warm water with canned renal diets, creating a mashed potatoes consistency
   - A homemade renal diet recipe formulated by a veterinary nutritionist (for patients that refuse to eat commercial renal diets)
5. **Consider placing a feeding tube** if a patient is still reluctant to eat despite symptomatic and supportive care but is otherwise feeling well. This approach is particularly helpful in cats with CKD; they often thrive for years once adequate nutrition is provided.

How Does Enteric Dialysis Work?

Enteric dialysis allows excretion by a nonrenal mechanism of some wasteful products from protein metabolism. By adding certain types of fermentable fiber to the diet, this process can be enhanced. **Fermentable fiber** is a fuel source for certain types of intestinal bacteria.

Process *without* Fermentable Fiber

1. Normally, a small amount of urea is transported from the colonic blood supply into the gut's lumen.
2. In the lumen, intestinal bacteria hydrolyze urea into ammonia by producing the enzyme urease.
3. This ammonia is subsequently incorporated into bacterial protein; then excreted from the body when the animal defecates.

Process *with* Fermentable Fiber

1. When intestinal bacteria ferment dietary fiber:
   - Short-chain fatty acids (SCFAs) are produced
   - Bacterial numbers increase
   - Health of the colonic mucosa surface epithelium improves.
2. SCFAs, in turn, increase blood flow to the colon and urea presentation to the intestinal tract.
3. Increased bacterial proliferation maintains urea concentration gradient, allowing continued flow of urea from blood into the lumen and excretion via the intestine when the animal defecates.

of antioxidants are beneficial for dogs.

- Most recently, dietary protein restriction in dogs with CKD may be unnecessary as long as the diet fed is phosphorus restricted and supplemented with prebiotic fiber to promote enteric dialysis.[5]

It is important to keep in mind, though, that commercial therapeutic renal diets vary in their nutritional composition. ■

AA = arachidonic acid; AAFCO = Association of American Feed Control Officials; ALA = alpha-linolenic acid; CKD = chronic kidney disease; DMB = dry matter basis; EPA = eicosapentaenoic acid; FOS = fructooligosaccharide; GCP = glomerular capillary pressure; GFR = glomerular filtration rate; H = high; L = low; LA = linoleic acid; PUFA = polyunsaturated fatty acid; ROS = reactive oxygen species; SCFA = short-chain fatty acid

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