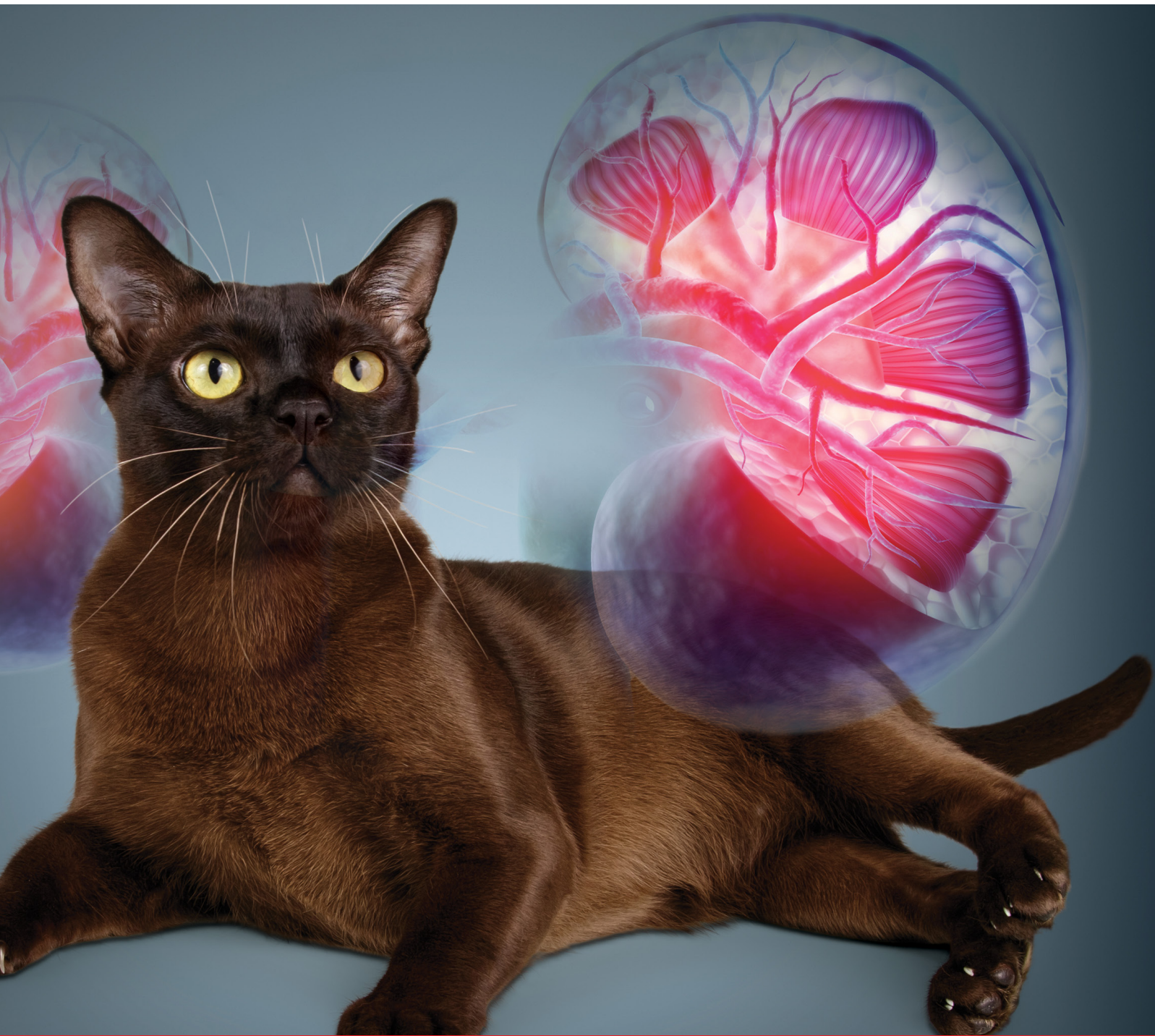


CHRONIC KIDNEY DISEASE IN CATS: Nutritional Management

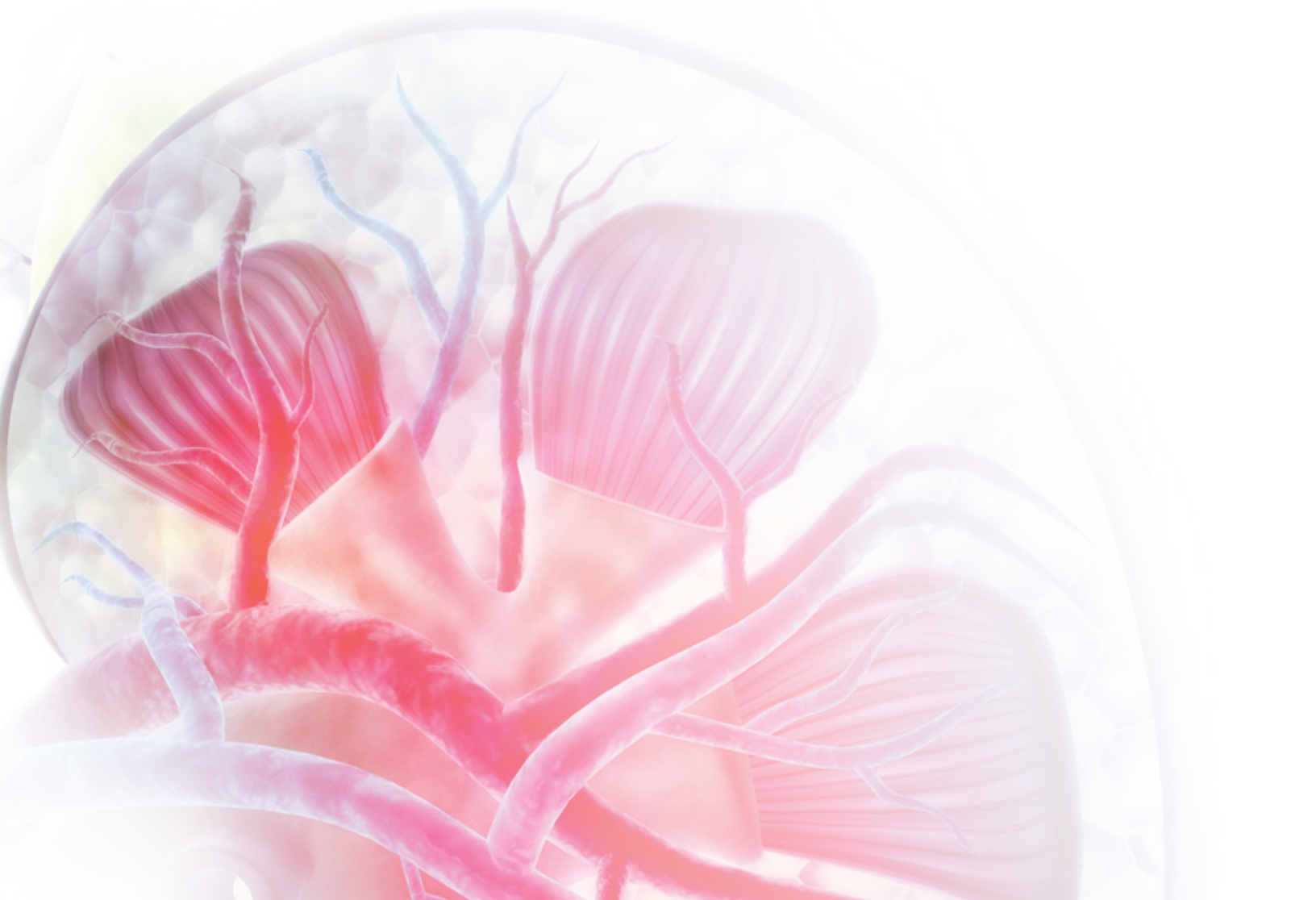


CHRONIC KIDNEY DISEASE IS A COMMON HEALTH CONCERN FOR CATS

While chronic kidney disease (CKD) can occur at any stage of life, its prevalence increases with age.^{1,2} Research has reported that cats have an approximately 20–40% greater risk of developing CKD with each passing year.^{1,3}

Although the disease cannot be cured, targeted nutritional strategies can have a beneficial impact in cats with CKD.⁴⁻⁷ Therapeutic renal diets may help slow disease progression, reduce signs of uremia, address homeostatic changes that result from decreased renal function, and improve the pet's quality of life and life span.

Ongoing research into biomarkers as well as other emerging areas of research may make earlier disease detection possible in the future and enable clinicians to diagnose and stage cats with CKD more accurately. These developments in turn may help further target nutritional and medical strategies to best meet the needs of each cat.



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HEALTHY KIDNEY FUNCTION

Healthy kidneys filter metabolic waste and help maintain the balance of fluids and electrolytes. They also help maintain acid-base balance, regulate phosphorus and potassium levels, produce the hormone erythropoietin, which stimulates red blood cell production, and influence blood pressure through the production of renin.

Nephrons are the functional units of the kidney. In the nephron, blood vessels from the body feed into the glomerulus, a high-pressure bundle of capillaries where the first step of filtration occurs. The resulting filtrate then passes through a series of tubules where additional substances are added to the filtrate or reabsorbed into the bloodstream before the fluid drains into collecting ducts that lead to the bladder.

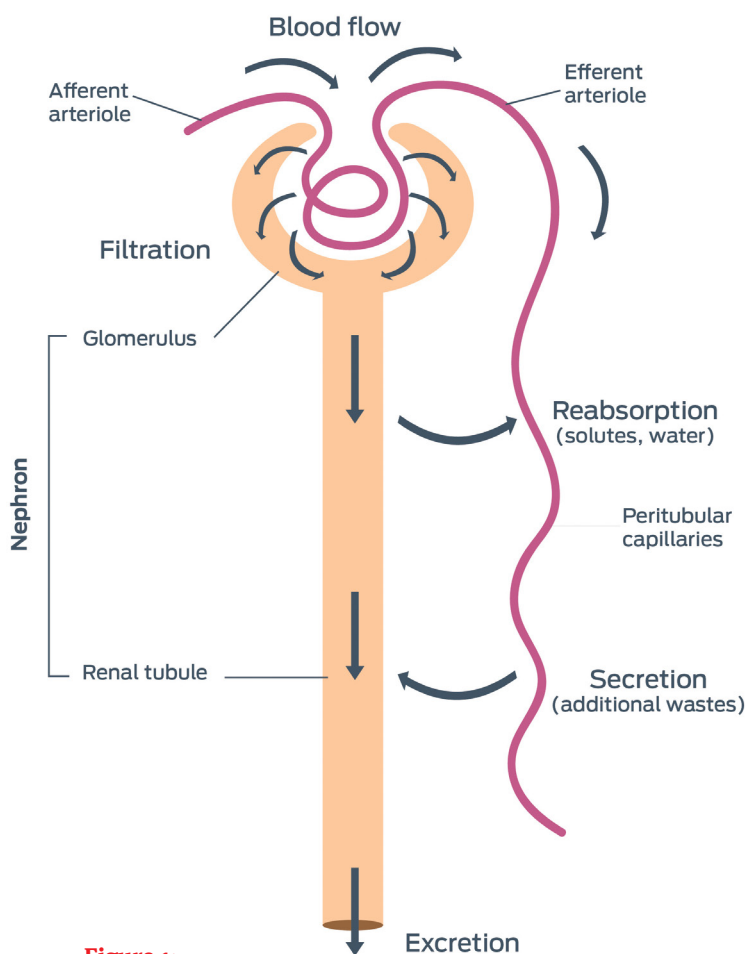


Figure 1:
Nephron

CHRONIC KIDNEY DISEASE

Chronic kidney disease is defined as abnormal renal structure or function, or both, that has persisted for 3 months or more.⁸

More than 50% of cases of CKD in cats are idiopathic.^{9,10} In most cats with CKD, the kidneys are damaged by inflammation and progressive fibrosis of the tubules.^{9,11-14} This is in contrast to CKD in dogs, in which primary glomerular disease is more common.¹⁵

Regardless of the inciting cause, CKD results in the progressive loss of nephrons and, as a result, kidney function. In early stages, undamaged nephrons compensate through hypertrophy, increased glomerular capillary pressure, and increased glomerular filtration rates (GFR) (hyperfiltration). However, this response cannot be maintained indefinitely and, over time, GFR declines. This slower rate leads to “leaky” filtration, resulting in rising serum levels of phosphorus and waste products—such as creatinine and uremic toxins—that should have been removed, while protein that should have been retained may spill into the urine.^{12,16}

CKD is usually diagnosed by persistent renal azotemia and inappropriately dilute urine supported by the presence of clinical signs, exam findings, and, potentially, imaging.⁸ Creatinine and blood urea nitrogen (BUN) are considered functional biomarkers and used as surrogate indicators of GFR.^{8,17}

By the time renal azotemia is evident in cats, at least 75% of kidney function is compromised,^{13,18-20} and thus, early CKD may be missed.^{13,18,19,21} The presence of early CKD should be suspected if creatinine, although within normal reference range, increases by more than 15–20% from baseline or increases repeatedly and the elevations persist.^{8,22-24}

Symmetric dimethylarginine (SDMA) is another functional biomarker—one that has been shown to have a linear association with creatinine but helps detect disease earlier.^{17,21} A retrospective study showed that SDMA was

elevated in 17 of 21 cats with CKD at an average of 17 months prior to elevated creatinine.²¹ None of the cats with CKD had an increased creatinine before an increased SDMA. Sensitivity of serum SDMA was 100% compared to 17% for serum creatinine.

Additionally, SDMA is not affected by lean body mass (LBM) while creatinine can be falsely low in cats with muscle loss.^{8,25} A study found that geriatric cats (over 15 years of age) had less lean body mass, lower GFR, higher serum SDMA, and lower serum creatinine (likely due to the loss of LBM) than cats under 12 years old.²⁵ SDMA was the better indicator of kidney function in this study.

The levels of markers, along with signs of disease, help gauge the cat's condition.

Staging CKD

The International Renal Interest Society (IRIS) developed guidelines for staging CKD based on fasting blood creatinine and SDMA levels—measured at least twice in a stable and hydrated patient—after CKD is diagnosed.²⁶ These guidelines were adopted by the American and European Societies of Veterinary Nephrology and Urology in 2003.²⁷ The IRIS Board reviews and updates the guidelines at least once a year.²⁷

The IRIS guidelines then sub-stage CKD based on the presence or absence of proteinuria and hypertension:

Urine protein-to-creatinine ratio	Proteinuria sub-stage
< 0.2	Non-proteinuric
0.2–0.4	Borderline proteinuric
> 0.4	Proteinuric

Systolic blood pressure (mm Hg)	Blood pressure sub-stage
< 140	Normotensive
140–159	Prehypertensive
160–179	Hypertensive
≥ 180	Severely hypertensive

Staging and sub-staging help guide treatment with the goal to improve outcome, as well as help predict prognosis.²⁸ Predictably, the stage at the time of diagnosis affects median survival.²⁸ In a retrospective study in which cats with CKD were staged based on serum creatinine and were not sub-staged, cats in stage 2b (in this study, defined as having serum creatinine of 2.3–2.8 mg/dL) lived a significantly longer time versus cats in later stages: a median of 1,151 days compared to 778 days for stage 3 cats and 103 days for cats in stage 4.²⁸

Blood concentrations of	Feline CKD IRIS Stage			
	1	2	3	4
Creatinine	< 1.6 mg/dL < 140 µmol/L	1.6–2.8 mg/dL 140–250 µmol/L	2.9–5.0 mg/dL 251–440 µmol/L	> 5.0 mg/dL > 440 µmol/L
SDMA	< 18 µg/dl	18–25 µg/dl	26–38 µg/dl	> 38 µg/dl

NUTRITIONAL OBJECTIVES

At any stage of renal disease, the objectives of dietary management are to meet the cat’s overall energy and nutrient needs, slow disease progression, reduce signs of uremia, address changes in homeostasis that result from inadequate kidney function, and improve quality of life as well as life span.^{8,12,16} Nutrition should be tailored to the individual cat’s needs and response to management.²⁹ Individualizing the nutrition plan helps address weight loss and loss of lean body mass (LBM), or if the cat has not lost weight or muscle mass, helps maintain body condition and muscle condition.

Whether CKD progresses and its rate of progression vary among individual cats,^{9,13,14,28,30,31} Cats may live with the disease for years, emphasizing the importance of providing adequate nutrition over the span of treatment.^{8,12,16}

MAINTAINING BODY WEIGHT AND LEAN BODY MASS

Maintaining body weight and LBM requires adequate calorie and protein intake.

Fat and protein digestibility may be decreased in healthy older cats, with research showing cats over 8 years old affected.³² In cats over 14 years of age, 30% had decreased fat digestibility and 20% had reduced protein digestibility, with some cats having reduced digestibility of both fat and protein. Results suggest that older cats may have increased calorie and protein needs.

Although studies show that cats can metabolically accommodate a range of protein levels once minimum protein needs are met, an inadequate intake of protein leads to loss of LBM.³³ Conversely, increased protein intake can reduce the loss of LBM.³⁴⁻³⁶

With age, cats naturally lose LBM.³⁷ Cats with CKD may lose even more through metabolic changes or cachexia—the excessive loss of muscle in association with disease—which may alter strength, immune function, and overall survival.³⁷ In both aging cats and those with CKD, losses in LBM or body weight are associated with increased mortality.^{28,38-40} Low body condition score has also been associated with decreased survival in dogs with CKD.⁴¹

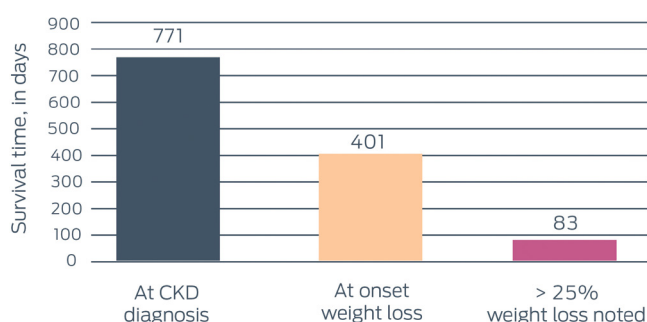


Figure 2: Survival time and weight loss in cats with CKD²⁸

Among 569 cats with CKD, those with a body weight at diagnosis above the group median of **4.2 kg** had a significantly longer survival time than those at weights below this median.³⁸



The loss of body weight and LBM often begins before CKD is diagnosed in cats.³⁸ Thus, preserving LBM and body weight is a key nutritional goal for these felines. The importance of LBM preservation, the evidence suggesting older cats have increased protein needs, and the increased risk for mortality associated with loss of body weight and LBM together suggest that protein restriction may not provide optimal nutrition for cats with early-stage CKD. (See further discussion under Protein in next section.)

TARGETED NUTRITIONAL STRATEGIES

Numerous studies have shown that therapeutic “renal diets” favor better clinical outcomes and can extend life span in cats with moderate to severe CKD when compared to feeding adult maintenance diets.⁴⁷ Therapeutic renal diets are recommended for CKD cats in IRIS stages 2–4,^{8,42} although some studies suggest benefit from feeding a therapeutic renal diet to cats in stage 1 CKD.^{43,44}

The modifications to therapeutic renal diets typically include reduced phosphorus and protein, and added alkalinizing agents, potassium, omega-3 fatty acids, and antioxidants.^{4,6-8,42,45,46}

Phosphorus

The kidney is the primary route of phosphorus excretion. During progression of CKD, without restriction of phosphorus in the diet, the gradual decline in renal phosphorus clearance leads to increases in blood phosphorus concentrations.^{47,48}

Even before the onset of hyperphosphatemia, rising blood phosphorus concentrations trigger increased secretion of fibroblast growth factor-23 (FGF-23), a protein secreted by bone cells that acts to increase excretion of phosphate in the urine.⁴⁸⁻⁵⁰ Additionally, rising blood phosphate triggers a response in the parathyroid glands, which balance calcium and phosphorus levels.⁴⁸⁻⁵¹

The parathyroid glands operate on a feedback system: High phosphorus in the bloodstream and low concentrations of ionized calcium (the biologically active form of calcium)⁵² stimulate increased parathyroid hormone (PTH) levels,^{48,50,53,54} leading to increased calcium reabsorption in the renal tubules, urinary phosphate excretion, and calcium and phosphorus resorption from bone.^{48-51,53} Renal secondary hyperparathyroidism, with elevated PTH concentrations, has been reported in 84% of cats with CKD, with prevalence and severity increasing as CKD progresses towards end-stage disease.⁵⁵

Plasma phosphate concentration is a predictor for progression of feline CKD.^{11,30,56} In cats with CKD between IRIS stage 2–4, research showed that a 0.32 mmol/L (1 mg/dL) increase in plasma phosphorus was correlated with a 41% higher risk of progression (where progression was defined as an at least 25% increase in plasma creatinine within a year after diagnosis).³⁰

Minimizing phosphorus retention and hyperphosphatemia appears to slow progression of CKD and prolong survival.^{30,46,57} For these reasons, correction or prevention of hyperphosphatemia is a primary concern in the management of CKD. Historically, this has been approached through restricting protein. Many protein ingredients have a high phosphorus content;^{16,58} therefore, reducing protein intake may reduce phosphorus intake.^{16,58} In cats with IRIS stage 2 through 4 CKD that were hyperphosphatemic, feeding phosphate- and protein-restricted diets (commercial therapeutic renal diets) significantly decreased plasma phosphate and FGF-23 concentrations.⁵

However, it is possible to formulate diets with lower phosphorus without restricting dietary protein.^{29,59} A study in cats with CKD compared a diet with phosphorus at maintenance concentrations (1.56% phosphorus, dry matter basis) to a restricted phosphorus diet (0.42% phosphorus, dry matter basis).⁴⁶ Results showed that lower levels of phosphorus reduced fibrosis, mineralization, and other adverse effects on the kidneys. However, there were no significant changes in measures of renal function in either group.

Phosphate binders may aid in reducing blood phosphate accumulations in CKD when feeding a phosphate-restricted diet is not sufficient to maintain phosphorus below the upper limit of the target range recommended by IRIS.^{8,60} Phosphate binders are also particularly useful in cats that refuse to eat a therapeutic renal diet.⁸ As the name implies, phosphate binders bind and “trap” dietary phosphate in the gut before it is absorbed, via formation of unabsorbable compounds that are then excreted in the feces.⁶⁰

IRIS stage of CKD	IRIS target range for plasma phosphate concentration ⁴²
1	0.9–1.5 mmol/L (2.7–4.6 mg/dL)
2	0.9–1.5 mmol/L (2.7–4.6 mg/dL)
3	0.9–1.6 mmol/L (2.7–5.0 mg/dL)
4	0.9–1.9 mmol/L (2.7–6.0 mg/dL)

In a model of CKD, researchers showed that cats fed maintenance diets and phosphate binders demonstrated decreases in serum phosphate and PTH levels.⁶¹ A phosphate binder containing calcium carbonate and chitosan significantly reduced plasma phosphorus and urea levels in geriatric cats with CKD; no significant changes were noted in plasma calcium levels.⁶²

Cats with CKD fed a renal diet with or without a phosphate binder (added when phosphorus control was insufficient on the therapeutic diet alone) had a significant decrease in plasma urea and phosphate while CKD cats fed a maintenance diet did not.⁴ Plasma PTH significantly increased in cats fed the maintenance diet, while the phosphorus-restricted cats showed a trend towards a decrease in plasma PTH concentration.⁴

Since phosphate binders bind phosphate from the food, they should be given at or near mealtime.^{60,63} Initial dosage is based on the severity of hyperphosphatemia and on the concentration of phosphorus in the pet's diet. Dosage is then adjusted based on effect.^{60,63} Constipation is a potential side effect associated with phosphate binders.^{16,60}

Protein

The primary rationale for restricting dietary protein in cats with CKD is to reduce the accumulation of nitrogenous wastes—an accumulation that may result in clinical signs of uremia, e.g., nausea and vomiting. However, weight loss, cachexia, and protein malnutrition should also be avoided. (See earlier discussion under Maintaining Body Weight and Lean Body Mass.) While studies clearly show that therapeutic renal diets have a positive impact on cats with CKD, the impact of protein restriction is not defined.

Among renal diets, protein is only one variable. In studies intended to evaluate effects of diet on renal function, the diets varied not only in protein, but also phosphorus and other minerals, fatty acids, and buffering agents, all of which can affect kidney function.^{47,64,65}

Several studies have suggested that protein does not contribute to progression of renal disease. In one study, cats with CKD fed a diet with 51.7% protein on dry matter basis had a significantly higher mean serum urea nitrogen and a significantly lower mean urine specific gravity than cats fed a diet with 27.6% protein.⁶⁴ However, many of the cats fed the high-protein diet also developed hypokalemia because the diet was deficient in potassium; low potassium levels have a negative impact on the kidneys and can induce kidney disease.⁶⁶ By the time the potassium deficiency was corrected in the study, the cats had numerous markers of advanced CKD, which then improved as the study progressed. Further, cats fed the low-protein diet consumed fewer calories than cats eating the high-protein diet. Due to these confounding factors, any effects from protein levels could not be confirmed.

To tease out the effects of protein on CKD, Finco et al. studied four groups of cats with CKD that were fed diets with different protein and calorie amounts.⁶⁵ High protein intake did not affect CKD progression relative to low protein intake.

Although CKD in dogs is different from the disease in cats, a two-year study of dietary phosphorus and protein levels in dogs with CKD showed that survival was longer with low-phosphorus diets.⁶⁷ The level of protein did not adversely affect survival, GFR, or renal morphology by the end of the study.

Nutritional management can help cats live with CKD for many years. The challenge is to balance the unique nutrient needs of cats with dietary modifications that will help reduce clinical signs and slow progression of disease.

Studies suggest that higher dietary protein levels promote optimal body condition in aging cats and help reduce the natural, age-related loss of lean body mass.⁶⁸ In early-stage CKD, higher levels of protein may help reduce loss of lean body mass and the higher mortality rates associated with loss of lean body mass in aging cats with CKD.^{34-36,40} However, as CKD progresses, more moderate levels of protein may be needed to reduce signs of uremia while striving to maintain calorie intake and body weight.

The Significance of Proteinuria

While small amounts of protein may be present in the urine of healthy cats, when excessive amounts of protein are found, it is known as proteinuria. (See guidelines for sub-staging based on degree of proteinuria under the Staging CKD in Chronic Kidney Disease section.) CKD-associated proteinuria results from:^{13,69-72}

- Damage to or changes in permeability (“permeability”) of the glomerular filtration barrier, allowing excessive amounts of protein to cross.
- Lesions that compromise the ability of the proximal tubular epithelial cells to reabsorb the filtered protein. A lower degree of proteinuria is typical for tubular lesions versus lesions in the glomerular filtration barrier.
- Lesions affecting both the glomerular filtration barrier and the tubular epithelial cells.

Although there is not enough data to accurately determine incidence, evidence thus far suggests that most cats with CKD are not proteinuric.⁸ Those cats with proteinuria usually have milder proteinuria compared to dogs and humans with CKD.⁹ This is likely due to cats typically having primary tubulointerstitial disease versus primary glomerular disease more common in dogs and humans.^{9,11,15}

Glomerular disease in people with CKD is most often secondary to diabetes, hypertension, or other problems that have already compromised overall health and kidney function.^{9,73} In people with renal injury, protein intake is correlated with increased proteinuria, and dietary protein restriction with decreased proteinuria.⁷⁴⁻⁷⁷

However, when cats with CKD were fed varying levels of dietary protein, the degree of proteinuria was unrelated to protein intake.^{7,65} Additionally, a pair of studies that used angiotensin-converting enzyme (ACE) inhibitors to manage proteinuric CKD cats showed that reductions in proteinuria were independent of protein intake.^{78,79}

Even though it is typically mild, proteinuria has been shown to be a marker for CKD in cats and should be addressed:⁷⁰

- Research has shown that healthy senior cats with proteinuria were more likely to become azotemic within the next year than cats that were not proteinuric.⁸⁰
- Proteinuria is associated with CKD progression.^{11,30,81} Cats in IRIS stage 2–4 CKD with proteinuria were more likely to progress (defined as $\geq 25\%$ increase in creatinine) within a year than those that were not proteinuric at baseline.³⁰
 - It remains unknown as to whether proteinuria is only a marker indicating the severity of tubulointerstitial inflammation or an active contributor to progression. Progression could occur via the excess filtered protein reaching and overwhelming the ability of the proximal tubular epithelial cells to reabsorb the protein, which could lead to secretion of cytokines and chemokines from the cells and ultimately promote tubulointerstitial inflammation.^{14,30,70}
- The degree of proteinuria is a poor prognostic indicator for survival in cats with CKD.^{14,82,83} Research showed that the hazard ratio for death or euthanasia was 2.9 for CKD cats with borderline proteinuria at baseline (study enrollment) compared to non-proteinuric CKD cats.¹⁴ The hazard ratio was 4.0 for CKD cats that were proteinuric at baseline compared to non-proteinuric CKD cats.

Alkalinizing Buffers

The kidneys maintain acid-base balance in the body by reabsorbing bicarbonate in the renal tubules and eliminating acids derived from the diet (especially sulfur-containing amino acids) and from metabolism.¹² When GFR decreases in CKD, acids are retained in the bloodstream, which may overwhelm the body's bicarbonate buffering capacity and result in metabolic acidosis.^{12,16} Associated clinical signs include vomiting, anorexia, and lethargy.⁸⁴

Metabolic acidosis appears more frequently in cats with advanced disease.^{85,86} One study reported just over 50% of cats with plasma creatinine ≥ 400 $\mu\text{mol/L}$ were acidotic compared to no cats with mild disease (plasma creatinine ≤ 250 $\mu\text{mol/L}$) and only 15% of those with moderate disease (plasma creatinine between 251 and 399 $\mu\text{mol/L}$).⁸⁶ Therapeutic renal diets often contain an alkalinizing buffer, such as potassium citrate, potassium chloride, and/or calcium carbonate.^{16,59} An alkalinizing agent may be supplemented in addition to the diet if needed.^{16,59}

Potassium

Hypokalemia has been reported in approximately 20–30% of cats with CKD.^{13,59} Hypokalemia may occur for several reasons, including poor appetite, metabolic acidosis, and/or chronic stimulation of the renin-angiotensin-aldosterone system (RAAS) as is believed to occur in CKD. During RAAS activation, aldosterone acts on the kidneys to promote potassium excretion while promoting sodium and water reabsorption.^{29,59,84,87} Higher levels of potassium are found in therapeutic renal diets.⁵⁹ Potassium is also available in a supplement form (e.g., in a powder, tablet, gel) as potassium gluconate or potassium citrate.^{16,59}

Omega-3 Fatty Acids

Research has explored the benefits of supplementing the anti-inflammatory omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) to cats with CKD. A retrospective study found that cats with CKD fed therapeutic renal diets had longer survival times than cats fed owner-selected maintenance diets.⁶ Of note, the cats fed the therapeutic diet containing the highest level of EPA

out of the seven therapeutic diets evaluated survived the longest—a median of 23 months compared to 7 months for cats fed the owner-selected maintenance diets.

Fiber/Prebiotics

Supplementation with prebiotics has been shown to reduce circulating levels of uremic toxins in cats with CKD.⁸⁸ Research in other species suggests that this decrease may occur due to a shift in the gut microbiome, resulting in fewer protein-fermenting bacteria, and by improving damage to the gut epithelial tight junctions.⁸⁹ (See further discussion in The Gut-Kidney Axis section.) However, fiber can decrease nutrient digestibility and decrease the energy density of a diet, so high-fiber diets are not recommended for patients with CKD.

Antioxidants

Research suggests that increased oxidative stress plays a role in the pathogenesis of feline CKD.^{90,91} Results of one study showed that feeding cats with CKD a diet enriched with antioxidants (vitamins E and C and beta-carotene) reduced several indicators of oxidative stress.⁹² The most beneficial antioxidants and the most effective inclusion concentrations of antioxidants are not yet known.⁹³

ADDRESSING POOR APPETITE

Ensuring adequate energy intake is a crucial part of nutritional management of any disease, including CKD.^{8,29,45} However, in a survey of CKD cat owners, 43% reported that their cat had an abnormal appetite.⁹⁴

A cat with CKD may exhibit inappetence due to resistance to a dietary change.⁸ To facilitate the diet change, a cat with CKD ideally should be transitioned to a therapeutic renal diet prior to development of nausea or other signs, i.e., by early IRIS stage 2 CKD.^{8,16,95} A gradual transition, typically over 2–4 weeks in cats with CKD, may help with acceptance of the new diet.^{29,93,95}

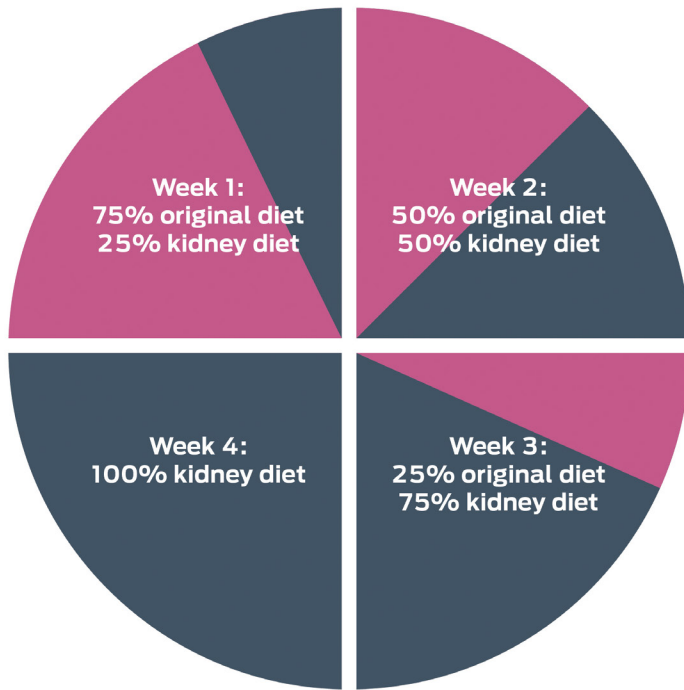


Figure 3:

An example protocol for transitioning a cat with CKD to a renal diet. The exact protocol needed will depend on the cat. Some cats may readily accept the new diet, allowing for a faster transition, while others may need an even slower transition.²⁹

Separate bowls for the current food and the renal diet should be used; mixing the foods in the same bowl is not advised.⁹³ This is a stress-reducing tactic that allows cats to choose between the foods rather than having the change imposed upon them.⁹⁵

A small amount of very palatable food, or palatable probiotics, flavored hydration supplements, or dry cat treats, can be added to a therapeutic diet to increase acceptance during the transition phase.^{29,63} Added calories that are not complete and balanced should account for no more than 10% of daily intake.²⁹

To avoid development of a conditioned taste aversion, a therapeutic renal diet should not be introduced when the cat is hospitalized.^{29,93,95} In hospitalized cats, for short-term feeding only, a complete and balanced highly palatable, highly digestible, energy-dense diet is appropriate, avoiding any of the cat's favorite foods.

If both wet and dry commercial renal diets from multiple pet food manufacturers have been offered to and refused by a cat with CKD, a home-cooked renal diet formulated by a veterinary nutritionist is another option.⁸ Feeding home-cooked diets can be challenging in cats in general due to, e.g., owner compliance (e.g., changing the recipe), supplement acceptance, and the potential for cats to selectively eat only the protein source.

In cases in which a cat with CKD will not accept a therapeutic renal diet, a feeding tube may be placed through which to provide a therapeutic renal diet.²⁹ Alternatively, some senior diets may have a reduced level of phosphorus relative to the cat's previous maintenance diet and could be considered.⁸ The manufacturers of the diets should be contacted to obtain the phosphorus concentration (g/100 kcal preferred for comparison). However, since all over-the-counter diets must meet maintenance minimum requirements for phosphorus, a level that is higher than what is recommended for cats with CKD, this is not an ideal option. A phosphate binder may be beneficial.⁸

Cats in more advanced stages of CKD are more likely to have a poor appetite.^{8,29} In these cases, interventions that may help increase food intake include:

- Nausea should be addressed.^{29,96}
- Appetite stimulants can be administered.²⁹
- Smaller meals, especially with wet food, should be offered more frequently.²⁹
- Food can be offered at different temperatures, e.g., at room temperature or gently warmed, as the cat prefers.²⁹
- Even when feeding only one food, more than one bowl of food can be offered.

- An endpoint to mealtimes should be set to prevent constant exposure to food odors that may promote nausea or impact future consumption.
- Variety and novelty (when possible) may increase appetite.²⁹
- Stress should be avoided as much as possible.^{29,97} In hospitalized cats, creating a positive environment, e.g., by having the owner bring an item from home that smells familiar, may help reduce stress.⁹⁷
- If very rewarding to the cat, petting, grooming, or other social interaction may stimulate the cat to eat.²⁹ If effective, the cat will eat after satiated on the interaction.
- Again, if rewarding to the cat, the owner or, when the cat is hospitalized, a well-liked member of the veterinary team can be nearby during mealtime but should not hover over the cat. At home, feeding the cat when and where the human members of the household are eating may help.
- Multiple options for feeding dishes, e.g., bowl and plate, can be offered to determine if the cat has a preference. The containers should not retain odors. Typically, this would be a stainless steel or ceramic, not a plastic, dish. Bowls, plates, or other containers should be cleaned before each feeding.
- Food should be stored in airtight packaging to ensure freshness and to avoid other odors or tastes transferring onto food.

For cats that remain inappetent despite the above interventions, a feeding tube should be discussed with the owner and placed to ensure sufficient caloric intake over the long term.^{8,93,97}

ENSURING ADEQUATE HYDRATION

Cats with CKD are at risk for dehydration. They are often polyuric (secondary to hyposthenuria) and polydipsic. Dehydration results when more fluid is lost than consumed. This affects acid-base and electrolyte balance and often manifests with clinical signs such as lethargy, anorexia, and/or constipation.^{16,29,93,98} Dehydration may also impair perfusion of renal tissues, which leads to progression of disease.^{12,29,93}

Water intake may be promoted by feeding a wet renal diet or a dry food with added water, and/or offering flavored hydration supplements.²⁹ Purina researchers found healthy cats offered a specially-formulated, nutrient-enriched, flavored water supplement consumed more water.^{99,100}

The use of a water fountain or other source of free-falling water, e.g., water from a tap, or circulating water may increase water intake. Research with healthy cats has suggested that individual cats may prefer one method of water delivery over another.¹⁰¹ Thus initially, options should be offered to identify the preferred option if the cat has one.

Other recommendations include offering multiple water bowls, using wide bowls (so that the cat's whiskers do not touch the sides of the bowl), and using stainless steel or ceramic bowls. Regardless of how water is offered, it should always be clean and fresh.

Subcutaneous fluids on a periodic basis at home or in the clinic may help maintain hydration. Intravenous fluids are indicated for cats in advanced stages. In cats with a feeding tube, water may be provided via the feeding tube.

EMERGING SERUM AND URINARY BIOMARKERS

Biomarkers are used to diagnose CKD, monitor progression and response to management, and gauge prognosis. Early detection of CKD is valuable since this presents the opportunity for early intervention, which may improve prognosis.¹⁰² Key measures currently used to monitor CKD progression and response to management are blood creatinine, SDMA, urea nitrogen, phosphate, calcium, sodium, and potassium; hematocrit; as well as urine specific gravity and severity of proteinuria, if present.^{8,11,13,30,69,70,103} Prognosis is currently based on the IRIS stage and sub-stage.⁶³

A biomarker recently added to IRIS recommendations for monitoring of progression and management is FGF-23.⁴² Circulating FGF-23 levels appear to be a sensitive indicator of kidney function:

- In healthy non-azotemic senior cats (over 9 years of age), plasma FGF-23 levels were significantly higher at baseline in cats that became azotemic within the next 12 months versus cats that remained non-azotemic.¹⁰⁴ In another group of senior cats (healthy or with kidney disease), plasma FGF-23 concentrations had a negative exponential association with GFR.¹⁰⁴
- Measurement of serum FGF-23 may help detect disease in its earlier stages.^{2,105} Since increased secretion of FGF-23 in response to rising serum phosphate may initially maintain serum phosphate within normal reference range, elevated FGF-23 levels may be detected prior to development of hyperphosphatemia.^{2,105}

Research showed that serum FGF-23 was significantly higher in cats beginning at stage 1 of CKD compared to healthy controls.² This contrasted with a significantly elevated serum phosphorus only in stage 3 and 4 CKD cats compared to healthy control cats.

Results indicated that despite normal serum phosphorus levels, phosphate regulation is changed in early CKD.

Results suggest that measurement of FGF-23 could be useful in determining when in early CKD to institute phosphorus restriction (see Phosphorus under Targeted Nutritional Strategies).^{2,105}

- In another study of senior cats, plasma FGF-23 concentrations were significantly different between healthy controls, stage 2 CKD, stage 3 CKD, and stage 4 CKD cats.¹⁰⁶ Plasma FGF-23 concentrations also differed significantly within stage 2 and stage 3 cats between those with plasma phosphate concentrations within IRIS recommended levels and those with plasma phosphate above IRIS recommendations.
- A retrospective study linked a significant decline in plasma FGF-23 concentrations to feeding a therapeutic renal diet in feline CKD patients, whether or not the cats were hyperphosphatemic (as per IRIS targets for plasma phosphate concentrations at each stage) when the diet was started.⁵ However, plasma phosphate and PTH concentrations significantly declined only in those cats that were hyperphosphatemic at initiation of feeding the renal diet.

Results suggested that phosphate balance is affected by feeding a phosphate-restricted diet irrespective of significant alterations in plasma phosphate levels. Thus, FGF-23 levels may act as a marker not just for when to initiate phosphate restriction but also for whether phosphate is being restricted sufficiently.

- FGF-23 also may have prognostic potential.³ A retrospective study of azotemic senior CKD cats showed that a 10x higher plasma concentration of FGF-23 at the time of CKD diagnosis correlated with a nearly 3x risk of progression (defined as at least a 25% increase in plasma creatinine) within 1 year.³ The same study reported that as plasma FGF-23 concentrations at CKD diagnosis increased, duration of survival (all-cause mortality) decreased.
- The relationship between FGF-23 and progression or survival is not yet fully understood—researchers have questioned if FGF-23 is merely a marker or is a uremic

toxin contributing to progression of CKD.³ More studies are needed to understand the complex interactions of FGF-23 in the kidneys and parathyroid glands.

Biomarkers that have received interest but are not yet routinely recommended to diagnose CKD, evaluate progression, and/or assess prognosis include the following:

■ **PTH.** As would be expected, research has shown an association between PTH and phosphate concentrations in the circulation⁵⁵ and between PTH and FGF-23 concentrations.^{2,104} Plasma PTH and phosphate concentrations were significantly greater in cats with CKD than healthy controls.⁵⁵

One study has suggested that elevated PTH may be an early marker for development of CKD.¹⁰⁷ Despite a lack of significant differences between groups of healthy senior cats in plasma calcium and phosphate concentrations at baseline, cats that were azotemic at the follow-up evaluation one year later had had significantly higher plasma PTH values at baseline than those that remained non-azotemic.

■ **Indoxyl sulfate.** Bacteria in the colon metabolize unabsorbed nutrients. Fermentation of protein and amino acids by colonic bacteria yields metabolic waste products known as uremic toxins, such as indole, which is generated by metabolism of dietary tryptophan.¹⁰⁸

In health, indole and other uremic toxins are absorbed from the gut, potentially metabolized (indole is metabolized to indoxyl sulfate by the liver), and then excreted by the kidneys. However, a decreased GFR can cause uremic toxins to accumulate in the bloodstream at which point they may have adverse effects on the kidneys and throughout the body.¹⁰⁹⁻¹¹³

Indoxyl sulfate induces oxidative stress and plays a role in development of tubulointerstitial fibrosis.^{109,111} Thus, indoxyl sulfate is a biomarker of CKD and, as a uremic toxin, contributes to kidney damage.

Cats in IRIS stages 2–4 CKD were shown to have significantly higher circulating levels of indoxyl sulfate

than healthy senior cats.^{108,114} One study found that while plasma concentrations did not differ significantly between stage 2 and 3 cats, stage 4 cats had significantly higher levels of indoxyl sulfate than stage 2 and 3 cats.¹⁰⁸ Researchers also noted a significant association between plasma indoxyl and serum creatinine, BUN, and serum phosphorus concentrations.

Other research found that cats with azotemic CKD that progressed had significantly higher plasma levels of indoxyl sulfate in addition to lower hematocrit and hemoglobin, and higher serum phosphate at baseline than cats that did not progress.¹¹⁵ In this study, progression was defined as moving up one IRIS stage or having an increase in serum creatinine of at least 0.5 mg/dL within the same IRIS stage within 3 months. On a within-stage basis, cats in stage 2 or 3 that progressed had significantly higher indoxyl sulfate levels at baseline than cats in stage 2 or 3, respectively, that did not progress. Plasma indoxyl sulfate was judged to independently predict CKD progression.

In a retrospective study in which progression of CKD was defined as an increase in serum creatinine of at least 0.5 mg/dL or death or euthanasia within 3 months, stage 2 or 3 cats that progressed had significantly higher plasma indoxyl sulfate and FGF-23 than those cats that did not progress.¹¹⁶ While measuring either indoxyl sulfate or FGF-23 predicted progression, evaluating both biomarkers together provided a better gauge of progression versus using one or the other by itself.

■ **Transforming growth factor-beta (TGF-β).** Research found that levels of the profibrotic cytokine TGF-β in the urine were significantly higher in cats with CKD compared to healthy control cats.^{117,118} CKD cats could be in IRIS stages 2–4 based on study inclusion criteria. Evaluation of urinary TGF-β levels in stage 1 of CKD and comparison of levels in cats at different stages of CKD may reveal that urinary TGF-β is useful not only as a marker of CKD but as a biomarker of early disease and/or of disease progression, i.e., worsening of fibrosis.

■ **Interleukin-8 (IL-8).** IL-8 is secreted by inflammatory cells. As a chemokine, it promotes the infiltration of additional white blood cells to the area, thus contributing to the cycle of inflammation and fibrosis in the affected kidney(s).¹¹⁸

A study showed that urinary levels of IL-8 were significantly higher in cats with CKD versus healthy control cats.¹¹⁸ This study included only those cats with CKD stage 2 or above and did not compare urinary levels of IL-8 among different stages of CKD. Research measuring levels in stage 1 CKD and comparing levels among stages 1, 2, 3, and 4 of CKD may show that this biomarker is useful for early detection and/or to monitor progression of disease.

Urinary biomarkers known as injury biomarkers indicate active renal injury and/or indicate dysfunction due to previous or active injury.⁷² Injury biomarkers may help detect disease or progression of disease and could be used in combination with functional biomarkers, e.g., blood creatinine and SDMA.^{19,72,119}

■ **Heat shock protein-72.** Urinary levels of this injury biomarker were shown to be correlated with all-cause mortality in cats with CKD.¹¹⁹ Cats with a urinary heat shock protein-72-to-urinary creatinine ratio of less than or equal to 4.2 ng/mg survived significantly longer (median of 561 versus 112 days) than cats with a ratio above 4.2 ng/mg. Researchers suggested further investigation to determine if urinary heat shock protein-72 could also be useful as an indicator of early CKD and/or progression.

■ **Neutrophil gelatinase-associated lipocalin (NGAL).** Urinary NGAL is a biomarker indicating proximal tubular epithelial damage.¹²⁰ Research showed that urinary levels of NGAL and the urinary NGAL-to-creatinine ratio (UNCR) were significantly higher in cats with stage 3 or 4 CKD compared to healthy cats or

cats with stage 2 CKD.¹²¹ Levels did not differ between cats with stage 2 CKD and healthy controls. Thus, while increased in later-stage CKD, the biomarker did not detect early disease. Urinary NGAL and UNCR were significantly higher in CKD cats that progressed within one month (defined as an increase greater than 0.5 mg/dL in serum creatinine) than in those cats that did not progress.

Another study found that while urinary levels of NGAL did not differ between CKD and healthy control cats, UNCR was significantly higher in cats with stage 3 CKD compared to healthy cats or cats with stage 2 CKD.¹²² Results also showed the ratio was significantly higher in stage 4 CKD compared to all other groups.

While those studies were promising, more recent research evaluated only UNCR and found no significant differences between healthy cats and cats with CKD.¹²³ Additional research is necessary to determine whether urinary NGAL and/or UNCR are useful biomarkers for CKD in cats.

■ Research thus far suggests that neither serum nor urinary cystatin C is a useful biomarker in cats with CKD.^{120,124} One study showed that serum cystatin C had poor sensitivity (22% sensitivity versus 83% for serum creatinine in detecting reduced GFR), while urinary cystatin C could not be detected in nearly 30% of the cats with CKD.¹²⁴

In the future, use of biomarkers that may more accurately predict, assess, and monitor renal dysfunction may lead to more precise nutritional strategies to help cats with CKD live better, longer lives.

THE GUT-KIDNEY AXIS

A bidirectional relationship, known as the gut-kidney axis, exists between the intestinal tract and the kidneys.¹²⁵ As has been described in humans with CKD,¹²⁵⁻¹²⁸ CKD in cats is associated with gut dysbiosis.¹¹⁴ Reduced diversity and richness of fecal bacteria were reported in cats with IRIS stages 2–4 CKD versus healthy senior cats.¹¹⁴

As noted earlier (see Emerging Serum and Urinary Biomarkers section), uremic toxins may accumulate in the bloodstream in CKD secondary to decreased GFR. CKD-associated dysbiosis may also contribute to the elevated concentrations of uremic toxins in the circulation:

- Greater concentrations of uremic toxins may be produced due to altered fermentation of protein and amino acids secondary to dysbiosis.¹²⁹
- Dysbiosis may alter gut wall permeability (“leaky gut syndrome,” due, at least in part, to compromised gut epithelial tight junctions),^{127,130} allowing higher concentrations of uremic toxins to cross the gut wall and reach the circulation.¹²⁹ This also may permit the translocation of bacteria and bacterial endotoxins across the gut wall into the circulation.^{127,130}

The presence of increased concentrations of uremic toxins, bacteria, and bacterial endotoxins in the circulation promotes inflammation throughout the body, including in the kidneys, and may be a contributing factor to CKD progression.^{127,130}

Branched-chain short-chain fatty acids (SCFA) are also produced during fermentation of protein by colonic bacteria.¹³¹ The significance of this is:

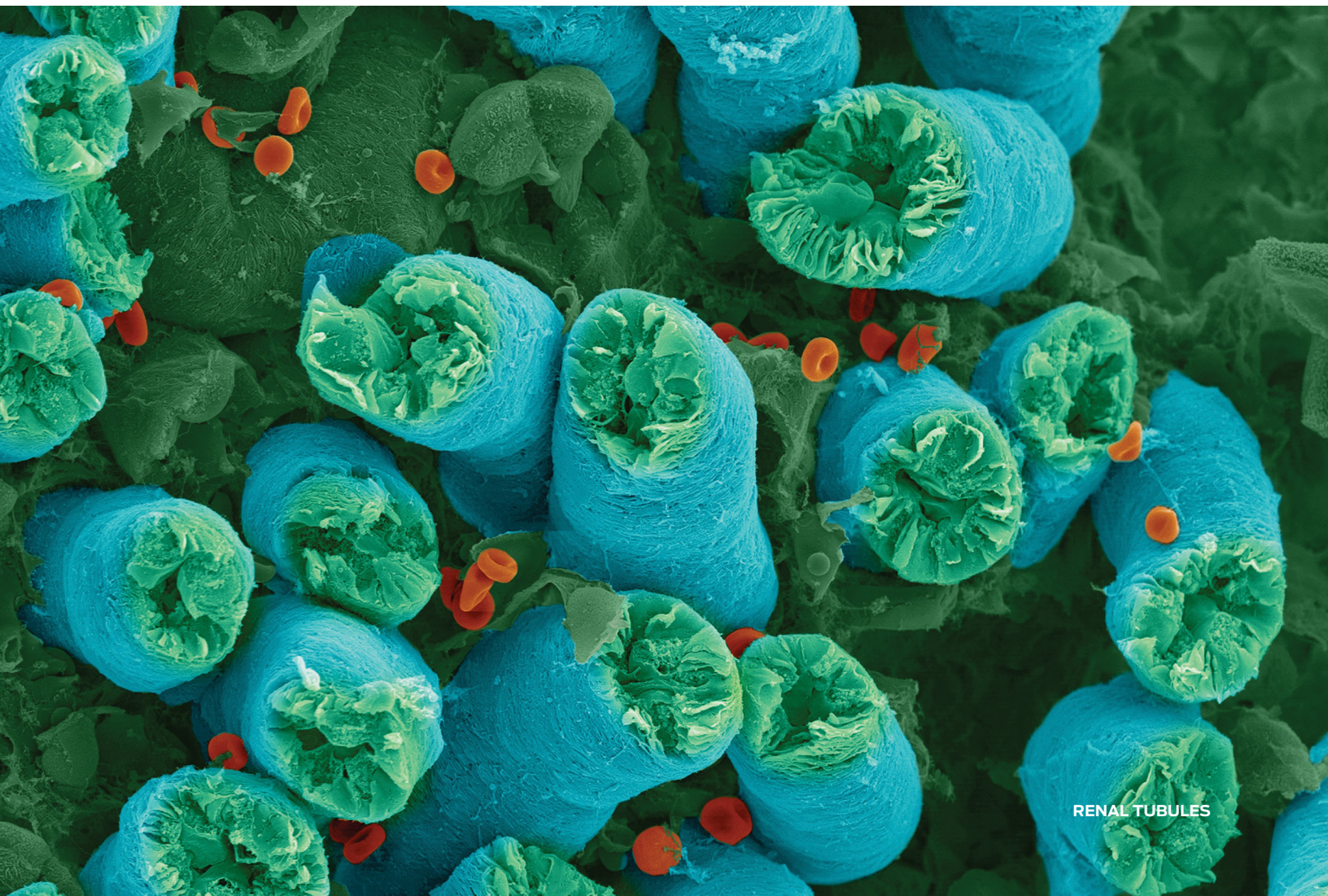
- Research showed that cats with CKD stages 2–4 had significantly higher fecal levels of isovaleric acid, a branched-chain SCFA, and significantly more muscle atrophy than healthy senior cats.¹³¹ Cats with muscle atrophy had significantly higher fecal levels of isovaleric acid, isobutyric acid (another branched-chain SCFA),

and total branched-chain SCFA compared to normal-muscled cats.

- A positive association was found between fecal total branched-chain SCFA levels and concentrations of serum creatinine, BUN, and serum p-cresol sulfate, a uremic toxin.¹³¹ Increased serum concentrations of uremic toxins¹¹⁴ and increased fecal concentrations of branched-chain SCFA suggest the presence of protein malassimilation in cats with CKD,¹³¹ which may affect dietary protein needs.

Researchers suggested that additional research be conducted exploring how the gut microbiome, branched-chain SCFA production in the colon, protein malassimilation, and CKD in cats are related.¹³¹ Future research in fecal biomarkers for feline CKD may also be needed.

Feeding therapeutic renal diets and other nutritional interventions tailored to the individual cat with CKD can play a key role in slowing disease progression, reducing signs of uremia, addressing homeostatic changes that result from decreased renal function, and improving quality of life as well as life span. New biomarker development and a deeper understanding of the extent and ramifications of the gut-kidney axis may enable even more targeted nutritional care for cats with CKD.



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