Controversies in Veterinary Nephrology: Renal Diets Are Indicated for Cats with International Renal Interest Society Chronic Kidney Disease Stages 2 to 4: The Con View

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KEYWORDS

- Feline
- Chronic kidney disease
- Therapeutic nutrition
- Protein
- Potassium
- Phosphorus
- Diet
- Malnutrition

KEY POINTS

- The ideal dietary nutrient composition to optimize the health of cats with chronic kidney disease (CKD) remains unclear.
- Limited research has been published regarding dietary management for cats with CKD; although some benefits were documented, there is inadequate evidence to support protein restriction.
- Phosphorus restriction seems to be of value in CKD, but inadequate data are available to determine the degree of restriction needed.
- Adequate studies have not been performed comparing the value of dietary modification with appropriate pharmaceutical interventions.
- Hypokalemia should be avoided and corrected and caloric intake to support ideal body and muscle condition should be maintained.

INTRODUCTION: PATHOPHYSIOLOGY OF FELINE CHRONIC KIDNEY DISEASES AND GOALS OF DIETARY MANAGEMENT

Three important principles to consider regarding dietary management of cats with chronic kidney disease (CKD) include (1) abnormalities in normal homeostasis produced by renal insufficiency are influenced by dietary intake, (2) the kidney is...
susceptible to self-perpetuating injury, which may be influenced by dietary modification, and (3) the responses of cats with CKD to dietary or pharmaceutical management will vary dramatically and individualized therapy with appropriate follow-up are required. This article considers these principles and the available evidence regarding dietary management of cats with CKD.

To understand the abnormalities in homeostasis, one must consider normal kidney functions and the impact of renal disease on those functions. The primary function of the kidney is to serve as a filter, retaining important substances and releasing toxic and unnecessary excess of metabolism into the urine. These functions can be disrupted in CKD. Etiologies of CKD include hypoxia, pyelonephritis, toxins, ureterolithiasis and nephrolithiasis, retroviral infection, morbillivirus infection, leptospirosis, glomerulonephritis, renal neoplasia, amyloidosis, and hypokalemic nephropathy, as well as congenital conditions. Unlike humans and dogs, primary glomerular disease is rare in cats; however, glomerular dysfunction may occur secondary to inflammatory conditions, (eg, immune-mediated, pancreatitis, triaditis), or lymphoma.

It is generally accepted that the ultimate/common histomorphologic endpoint in feline CKD is interstitial fibrosis. There seem to be multiple paths to this outcome as well as wide variations in the degree of expression. It is hypothesized that chronic renal injury results in inflammation and infiltration by inflammatory cells (most commonly lymphocytes and plasma cells). This inflammation stimulates the production of profibrotic mediators (including transforming growth factor-beta, upregulation of the renin-angiotensin-aldosterone system [RAAS], transglutaminase 2, and endothelin 1), which activate matrix-producing cells and initiate fibrogenesis. Newly formed myofibroblasts and transformed tubular epithelial cells perpetuate the process. Chronic hypoxia and oxidative stress also contribute to the process. Activation of the RAAS results in increased angiotensin II levels that result in efferent arteriolar vasoconstriction and glomerular hypertension. Excess protein in the glomerular filtrate is believed to be toxic to tubules, although it may not cause fibrosis directly; proteinuria may instead reflect decreased tubular uptake in affected kidneys. Taken together, and likely with elegant processes we do not yet understand, a self-perpetuating process occurs. However, renal pathology in cats seems to follow a different trajectory compared with that in dogs. Clinically, we see this as cats living much longer after a diagnosis of CKD compared with dogs; cats with CKD can live for several years.

Despite potential species differences and regardless of underlying etiology, it seems that progression of CKD is inevitable, although the rate of progression varies widely between cats, occurring over months to years. Identified risk factors contributing to decreased survival time include renal azotemia, hyperphosphatemia, urine protein:creatinine ratio of greater than 0.4 or greater than 0.2, decreased hemoglobin and hematocrit, and leukocytosis. Left untreated, systemic hypertension affects quality of life, increases risk of target organ damage, may contribute to endothelial dysfunction and arterial structural changes resulting in hypoxia, and may induce glomerular hypertension and proteinuria. When appropriately treated, however, it does not seem to contribute to progression of CKD. Similarly, urinary tract infections, despite potentially initiating the inflammatory process, are not recognized to contribute to progression. Plasma calcium, bicarbonate, and potassium levels may play a role in clinical disease, but are not recognized to affect progression.

By altering the load of dietary and metabolic metabolites reaching the kidney, it is thought to be possible to alter the trajectory of the ongoing damage. Thus, the current standard of care is to feed patients with CKD protein restricted diets that are further modified to be restricted in phosphorus and sodium, and supplemented with
potassium, B vitamins, antioxidants, and long-chain omega-3 fatty acids. Assuming this is appropriate for other species, does this dictum suit cats—obligatory carnivores—as well?

What is the significance of being an obligatory carnivore? Cats certainly require more protein than dogs, humans, or other omnivores do and, similar to mink, have been identified as being hypercarnivorous. Cats have adapted to metabolize a native diet that is extremely high in protein (~52% of calories) and low in carbohydrate without developing ketonemia. They readily use protein and amino acids to generate the glucose needed by their brains and cells. Yet, healthy cats are capable of dealing with a wide range of protein and carbohydrate intakes, and can metabolize carbohydrates to spare protein to a great extent, so long as their minimum protein needs are met. However, like other species when protein needs are not met, cats undergo a gradual loss of lean body mass (LBM), catabolizing muscle and other lean tissues to meet the needs for protein turnover and ongoing metabolic needs. This effect may be worsened in cats with CKD, because protein catabolism is increased and synthesis decreased in other species with CKD. Unknown is whether or not cats’ kidneys deal with the amino acids and nitrogen metabolites derived from catabolism of LBM differently than those derived from dietary protein.

Independent of protein, does the available evidence support the need for all of the recommended nutrient modifications found in commercial “renal” diets, or would a different nutrient profile be more appropriate for cats with CKD? Is restricting phosphorus and sodium, increasing the pH, adding potassium, B vitamins, antioxidants, and essential fatty acids warranted in this species? This article attempts to address these questions nutrient, by nutrient.

DIETARY MANAGEMENT IN CHRONIC KIDNEY DISEASE

Protein

Protein restriction has been recommended for patients with kidney disease for decades. Much of the evidence to support the practice of protein restriction comes from rodent or canine studies, and many of these studies used diets that differed in multiple nutrients, such as phosphorus, in addition to protein. There are few studies in cats, and even fewer not confounded by multiple nutrient differences among diets tested.

Two studies have been performed in cats with induced CKD, both using a five-sixths nephrectomy model. The Adams study evaluated diets containing either 27.6% or 51.7% protein (dry matter basis) fed over the course of 1 year. They reported that the group fed the higher protein diet had significantly higher inulin clearance, lower serum creatinine, and maintained body weight better than cats fed the lower protein diet. However, cats fed the higher protein diet developed greater renal pathology and had greater serum urea nitrogen concentrations compared with those fed the lower protein diet. Critically, however, the higher protein diet was deficient in potassium, as evidenced by more than one-half of the cats fed this diet developing clinical manifestations of hypokalemia. Hypokalemia is recognized to cause or contribute to renal dysfunction in cats. Potassium was supplemented after the first 3 months of the study, but markers of renal dysfunction including urine protein excretion were notably worse in this group by this time. Other differences between diet groups included calorie intake, with cats fed the lower protein diet consuming fewer calories. Reduced calorie intake has been suggested to have a protective effect regarding kidney...
function.\textsuperscript{27} Because of these confounding factors, it cannot be clearly determined if the renal pathology assessed at the end of the study was due to protein or due to other factors. A second study was conducted in cats to attempt to address this issue.\textsuperscript{25} Using the same five-sixths nephrectomy model in cats, the study was designed to control for both protein and calorie intake. Potassium intake was adequate in all cats in this study. Cats with CKD fed the high protein, high calorie diet maintained body weight, whereas those fed the low protein diet lost weight. Markers of renal function, including glomerular filtration rate (GFR) and serum creatinine, were better in cats fed the higher protein diets although these effects did not achieve statistical significance. There were no effects from diet on urine protein/creatinine ratios. Renal histopathology showed no effects from protein intake on tubular lesions, fibrosis or cellular infiltrate, and a mild, nonsignificant increase in mesangial matrix accumulation. However, greater calorie intake was associated with significantly greater cellular infiltrate and tubular lesions, with a nonsignificant trend toward increased fibrosis. Overall, the results of this study showed no association between higher protein intake and renal lesions, proteinuria, or decreased GFR, which tended to refute the findings of the Adams study. Given this, and because the diet model and study design were similar, one must wonder if the differences in results were due to some differences in the diets. Between the 2 studies, differences included protein sources, fat content, and changes in cats’ body weight, but the most obvious difference was the inadequate potassium intake and resulting hypokalemia in the Adams study.

No clinical studies in cats with naturally occurring CKD have been conducted where only dietary protein levels were compared although several studies evaluated protein restricted “renal” diets in cats with spontaneous CKD (Table 1). Two of these were either retrospective studies or nonrandomized studies. In the first of these, 50 cats with CKD were entered into the study.\textsuperscript{28} Among these, 29 cats were offered dry or canned commercial protein-restricted, phosphorus-restricted renal diets. For the other 21 cats, the renal diet was not fed either because the cat refused the diet or the owner refused the diet. This group was kept on commercial maintenance diets. Phosphorus binders were used as needed to control hyperphosphatemia in cats fed the renal diet, with 34% using a phosphorus binder, but were not offered for cats fed the maintenance diets. The combination of renal diet with phosphorus binders resulted in this group living longer and having lower phosphate and parathyroid hormone (PTH) concentrations. A retrospective study compared results in cats with CKD fed either commercial protein and phosphorus-restricted diets from several manufacturers, or other diets including commercial maintenance diets.\textsuperscript{29} Cats fed the renal diets survived longer compared with those fed maintenance diets.

Two randomized, controlled prospective clinical evaluating diets for cats with spontaneous CKD also have been published. The first of these included 35 cats randomly divided into uneven groups so that 25 cats were offered a low-protein renal diet and 10 cats received a control maintenance diet for 24 weeks.\textsuperscript{30} Cats fed the maintenance diet lost weight, showed increases in serum urea nitrogen and creatinine, and greater clinical deterioration compared with those fed the renal diet. In a subsequent study, 45 cats with International Renal Interest Society (IRIS) stage 2 or 3 were randomly assigned to a renal or maintenance diet and followed for 2 years.\textsuperscript{31} As in previous studies, cats fed the renal diet showed greater survival. Unfortunately, none of these studies specifically evaluated protein. Therefore, although these studies are often used to support the feeding of protein-restricted diets, one must consider the many differences among the diets. At this time, there is inadequate evidence to support the need to restrict protein in cats with CKD.
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<td>Plantinga et al, 2005</td>
<td>Retrospective, nonrandomized</td>
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<td>All renal diets resulted in prolonged median survival vs various diets</td>
<td>Compared multiple commercial renal diets vs various diets; suggested that diet highest in long chain fatty acids associated with best response</td>
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Abbreviations: CKD, chronic kidney disease; FGF-23, fibroblast growth factor-23; GFR, glomerular filtration rate; IRIS, International Renal Interest Society; NA, not applicable; phos, phosphorus; PTH, parathyroid hormone; RAAS, renin-angiotensin-aldosterone system.
It has been suggested that protein restriction will reduce proteinuria in patients with CKD. This is based on pathophysiologic reasoning that proteinuria damages tubules and results in interstitial inflammation.\textsuperscript{4,32,33} Because proteinuria is a recognized negative prognostic factor in cats with CKD, this could be important. Studies have evaluated reduction in proteinuria and impact on quality of life in naturally occurring feline CKD using pharmacologic agents: angiotensin-converting enzyme inhibitors\textsuperscript{10,12} and angiotensin receptor blocker.\textsuperscript{34} However, there is very limited evidence to support a benefit from restriction of dietary protein. There are 2 studies in dogs with X-linked hereditary nephropathies showing a reduction in proteinuria with dietary protein restriction,\textsuperscript{35,36} but no studies evaluating protein restriction on quality of life or survival in dogs with glomerular disease. In cats with surgically induced CKD fed protein restricted diets that caused hypokalemia, proteinuria was significantly greater than in cats fed a low-protein diet.\textsuperscript{24} However, once potassium supplementation was initiated, proteinuria began to decrease, returning to near baseline levels after several months. In another study using the same experimental model of CKD, a high protein, potassium-replete diet was not associated with an increase in proteinuria.\textsuperscript{25} Likewise, when cats with naturally occurring stage 2 and 3 CKD were fed a protein-restricted renal diet or maintenance diet, there was no difference in proteinuria.\textsuperscript{31} Thus, the evidence does not support a role for dietary protein restriction for the management of proteinuria in CKD cats.

The goal of dietary management in any disease condition is to provide balanced nutritional support for the patient while also addressing the clinical signs or reducing ongoing pathology from the disease. Given this, one must consider also the potential detrimental effects from protein-restricted diets in aging cats. Cats are obligate carnivores and have a basal protein requirement that is considerably greater than many other species, including dogs. In healthy subjects, even marginally inadequate protein intake contributes to reduced protein turnover and loss of LBM over time, whereas increased protein intake can result in increased LBM.\textsuperscript{37,38} Loss of LBM as a result of aging or catabolic diseases increases the risks of morbidity and mortality. In other species with CKD, endogenous protein synthesis is decreased and catabolism increased, and mortality in CKD patients is related to loss of muscle mass.\textsuperscript{20}

It is common for aging cats and cats with CKD to experience a loss of body weight and LBM.\textsuperscript{39–42} In cats with CKD, lower body weight is associated with increased mortality,\textsuperscript{8,42}, thus prevention or reversal of loss may be a reasonable goal as part of patient management. To date, there are no controlled studies showing that prevention of loss of body weight or LBM extends survival in CKD cats. However, in healthy aging cats, preservation of body weight and LBM was associated with reduced risk for mortality.\textsuperscript{41} Other research showed that increased dietary protein intake helps to slow or reduce the age-associated loss of LBM in cats.\textsuperscript{43} In that study, research cats (aged 7–17 years) fed lower protein diets (7.5–10.4 g protein/100 Kcal metabolizable energy) lost weight over the 12 month study, whereas those fed 12.75 g protein/100 Kcal metabolizable energy were better able to maintain body weight. Further, although initial age had a significant impact on the amount of protein intake needed to maintain LBM, cats fed more protein lost less LBM over time.\textsuperscript{43} Given that most cats with CKD are older cats, this questions the relative value of protein restriction in these patients. Other factors in patients with CKD that can influence loss of LBM include energy intake and metabolic acidosis. These issues are addressed in separate sections within this paper.

Based on the available evidence, protein restriction per se is not warranted in cats with CKD. If a commercial renal diet is fed for its other benefits, it is recommended to select a higher protein option. It is important to monitor for adequate intake and for
loss of body weight and LBM. A muscle mass score, such as that recommended by the World Small Animal Veterinary Association (www.wsava.org/guidelines/global-nutrition-guidelines) should be used to monitor changes. Should a decline be apparent, consideration should be given to feeding a higher protein diet and addressing other renal pathologies through use of available medications.

**Phosphorus**

Phosphorus retention and secondary hyperparathyroidism are common complications of feline CKD. In healthy animals, phosphorus balance is controlled predominantly via the kidneys. In CKD, phosphorus excretion is compromised, leading to an increase in PTH concentrations, decreased production of active 1,25-dihydroxyvitamin D, and increased fibroblast growth factor 23 (FGF-23), all of which help to increase phosphorus excretion. These mechanisms result in normalization of serum phosphorus concentrations in early CKD. As CKD progresses, serum phosphorus concentrations increase, despite continued increases in PTH and FGF-23. In cats with CKD, serum phosphorus concentrations are inversely associated with survival.

Several experimental studies have documented that controlling the increases in serum phosphorus, PTH and FGF-23 resulted in reduced renal pathology, morbidity and mortality in remnant kidney models of CKD (in rats, cats).

Dietary phosphate restriction was evaluated in cats with induced CKD. In that study, cats were fed diets with either 0.42% (dry basis) or 1.56% (dry basis) phosphorus for 65 to 343 days. Serum phosphorus and PTH concentrations were increased in cats fed the higher phosphorus diet, but neither diet had a measureable impact on progression of renal function during the study. However, kidneys from cats fed the higher phosphorus diet showed mineralization, fibrosis, and mononuclear cell infiltration, whereas those from cats fed the restricted phosphorus diet showed none of these changes. Subsequent studies in experimental models have shown similarly that renal injury is reduced with phosphorus restriction independent of dietary protein content.

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In addition to the studies on dietary phosphorus restriction, 1 study evaluated the use of a phosphate binder in cats with CKD, using a remnant kidney model. In this study, cats with stage 1 or 2 CKD fed a maintenance diet with a phosphorus binder.
had significantly lower serum phosphorus and PTH compared with those fed the same diet but without the phosphorus binder. The beneficial effects on serum phosphorus and PTH persisted throughout the 9-month study. There were no differences in serum creatinine, blood urea nitrogen, or GFR by time or treatment during the study.

The evidence supports a real benefit to controlling phosphorus, but many questions remain. Is there an optimum dietary concentration for renal diets? This question is further complicated by the fact that phosphorus availability can differ greatly based on the composition of the diet. For example, phosphorus from vegetarian diets is less bioavailable compared with meat-based diets, and phosphates from inorganic sources are more bioavailable compared with those from organic or meat sources. Is restriction of dietary phosphorus superior, in terms of cat well-being and progression of disease, compared with phosphate binders? Do these differ based on stage of CKD progression? Because it seems that PTH and FGF-23 are increased before serum phosphorus increases, should these substances be used as the markers advising the use of phosphate binding or restriction? If so, what would be the appropriate reference value? Given the numerous unanswered questions, at this time, no specific guidelines can be provided for optimum dietary phosphorus content. Dietary phosphate restriction or phosphate binders should be tailored to the individual patient to achieve a serum phosphorus concentration within the low normal range, as recommended by IRIS (http://iris-kidney.com/guidelines/recommendations.aspx).

**Sodium**

The main rationale for dietary sodium restriction is to manage hypertension. Hypertension is a common finding in cats with CKD and may contribute to the progression of renal disease. Hypertension seems to cause proteinuria, with a direct association between degrees of hypertension, proteinuria, and progression of renal lesions in dogs with experimentally induced renal failure. Although similar data are not available in cats, proteinuria is a negative prognostic factor in cats with CKD.

Limited evidence addresses the link, if any, between dietary sodium and blood pressure in cats. A single case report indicated that a cat with idiopathic hypertension had been fed a high sodium diet and that sodium restriction, along with pharmaceutical management, was used to manage the case successfully. However, no attempt was made to isolate any effects of sodium in that case. Multiple studies in cats have since shown no impact of dietary sodium ranging between 0.3% and 1.3% of diet dry matter on systemic blood pressure. On the contrary, restriction of sodium has been shown to activate the RAAS and may actually lead to progression of vascular, renal and cardiac lesions. Further, low sodium intake (50 mg/kg body weight) increased urinary potassium loss, which can contribute to renal injury.

High sodium intake has been suggested to cause renal damage independent of effects on blood pressure. In a study that included various groups of cats including 6 with mild renal insufficiency, a diet providing 1.2% sodium was associated with increases in serum creatinine and urea nitrogen during a 12-week trial. Other studies did not confirm this and, instead, showed no adverse effects from sodium at similar dietary amounts in studies lasting 6 months to 2 years. In a 6-month study that included 9 cats with mild renal insufficiency, there was no impact from dietary sodium (0.55% vs 1.1% diet dry matter). None of these studies reported adverse effects from high sodium intake on urine protein/creatinine ratios. On the contrary, the data showed numerical but nonsignificant decreases in urine protein/creatinine ratios with the higher sodium intakes.

Activation of the RAAS and increases in plasma aldosterone concentrations are recognized as a contributing factor to ongoing renal damage. This may be
associated with the increase in oxidative stress and increased secretion of inflammatory mediators recognized to occur in response to elevations in aldosterone and RAAS. 69,70 Although species-specific differences do exist regarding the link between RAAS and renal injury, aldosterone is increased in cats with CKD and activation of the RAAS does promote ongoing renal injury in cats with CKD. 65,67,88,71 In cats with experimentally induced CKD, plasma aldosterone was increased over healthy cats regardless of dietary sodium intake and was greatest in cats fed the lowest sodium diet. 65 Further, low dietary sodium was recognized as a risk factor for the development of CKD in cats. 72 Therefore, excessive restriction of dietary sodium, which stimulates the RAAS, should be avoided in cats with CKD.

What constitutes “excessive restriction” is, unfortunately, poorly defined. Among the studies cited, dietary sodium ranged from approximately 0.33% to approximately 1.3% sodium on a dry matter basis. All of these are in excess of the suggested minimum requirements for normal adult cats, 73 yet the lower intakes were associated with inappropriate kaliuresis, reduced the GFR, and increased aldosterone concentrations in CKD cats. 66 Whereas 1 report suggests possible detrimental effects from sodium at 1.2% of the diet in cats with existing CKD, other studies refute this finding. Therefore, we conclude that the evidence does not support feeding sodium-restricted diets to cats with CKD.

Fatty acids

Prostaglandins (PG) play an important role in renal function and sodium and water balance. By altering vascular tone in the kidneys, PG affect renal blood flow and GFR. 74,75 Specific PG production can be influenced by alterations in dietary fatty acids. Diets rich in long-chain omega-3 fatty acids will yield less PGE2 and thromboxane A-2, compared with diets rich omega-6 fatty acids. PGE2 helps to maintain renal blood flow and is generally considered to be beneficial. However, thromboxane A-2 decreases renal blood flow and GFR, a potentially detrimental effect. In humans, mice, and dogs, PG production is increased in CKD, although this has not been documented in cats.

In remnant kidney model dogs, omega-3 supplementation, (specifically eicosapentaenoic acid [EPA] and docosahexaenoic acid) at 15% of the diet, resulted in decreased intraglomerular hypertension, decreased proteinuria, maintenance of GFR, and increased survival. 76,77 Also, the dogs fed the EPA and docosahexaenoic acid–enhanced diet had decreased renal lesions relative to those fed omega-6 polyunsaturated fatty acid–enhanced diet. Similar data are not available for cats; however, these researchers did evaluate the impact of omega-3 and omega-6 fatty acids on renal function in healthy cats. Both renal blood flow and GFR were increased in cats fed the diet rich in omega-3 fatty acids. 78

The amount of omega-3 polyunsaturated fatty acid that is most effective for reducing inflammation is unknown in different species and may also depend on the degree and type of disease. Although omega-6 fatty acids are essential, excessive dietary omega-6 levels and a very high omega-6:omega-3 is suggested to contribute to or promote cardiovascular disease, cancer, autoimmune, and inflammatory diseases in humans. 79 Brown 5 reported benefits of supplementing both omega-6:omega-3 polyunsaturated fatty acids at 5:1 and antioxidants (vitamin E, carotenoids, and lutein) on reducing the rate of decline of GFR in a remnant kidney model with older Beagles.

One retrospective study compared survival of cats with CKD eating maintenance diets with those eating 1 of 7 commercially available renal diets. The renal diet associated with longest survival had the highest EPA concentration. 29 However, owing to the retrospective nature of the study, lack of consistency in management between
participating practitioners and clients, and other differences in the diets, causality could not be established.

Recent evidence has been presented prospectively evaluating serum fatty acids in cats with IRIS stages 2 to 4 CKD. Cats were fed either a renal diet or a maintenance diet and were compared with age-matched healthy cats fed the maintenance diet. No differences were found in serum EPA or docosahexaenoic acid levels between any of the 3 groups, suggesting in this small study that feeding a renal diet does not provide benefit through increased blood omega-3 concentrations.

To date all evidence is circumstantial for benefit of fatty acids in feline CKD. Given that cats typically do not develop glomerular disease, they may not benefit from omega-3 fatty acids. On the other hand, because proteinuria seems to be a significant risk factor in cats with CKD, and omega-3 fatty acids may reduce proteinuria in other species, additional research is warranted to determine if cats would benefit from omega-3 fatty acids.

**Potassium**

Hypokalemia occurs in 20% to 30% of cats with CKD. However, clinical hypokalemia develops only after there is depletion of body stores of potassium or when extracellular potassium is redistributed into cells, such as with metabolic alkalosis. Because CKD is often associated with metabolic acidosis, which causes potassium to be shifted out of the cells and into the plasma, developing hypokalemia may be masked until body stores are depleted. In 1 study of cats with CKD and normal serum potassium, muscle potassium content was low. Therefore, the incidence of subclinical potassium depletion in cats with CKD is not known.

The gain or loss of potassium is influenced by diet, but also by the RAAS, and by alterations in renal tubular resorption. Experimentally induced chronic metabolic acidosis can cause potassium depletion and hypokalemia. Multiple studies in cats fed acidifying diets showed that these lower serum potassium concentrations and increase the risk for development of hypokalemia. Further, acidifying diets that were also low in potassium reduced GRF by 20% in healthy cats, and induced renal failure in 3 of 9 previously healthy young cats. The low potassium, acidifying diets also resulted in a reduction in plasma renin activity and increase in aldosterone, which tended to return to normal with potassium supplementation. It was suggested that the effects of acidosis and potassium depletion might be additive in their adverse effects on the kidneys. Independent of acid–base balance, another study that was designed to evaluate the impact of protein restriction in cats with induced CKD identified worsened renal function in cats fed a potassium-depleting diet. Four of the 7 cats fed this diet developed hypokalemia.

Clinical studies evaluating potassium supplementation in cats with naturally occurring CKD are lacking. The only published study in cats with CKD recruited only cats with normal serum potassium and fed all cats a diet with abundant potassium. They found no benefit to additional potassium supplementation in this very small study. However, among all 7 cats provided with supplemental potassium gluconate, GRF increased or remained stable during the 6-month study compared with only 3 of the 4 treated with sodium gluconate. Likewise, serum creatinine remained stable and serum urea nitrogen decreased 8.3% in the potassium treated group, whereas creatinine increased by 8.3% and serum urea nitrogen increased by 17.5% in the other group.
Based on the available evidence, provision of adequate potassium in a nonacidifying diet is important for renal function. However, because hyperkalemia occasionally occurs in cats with CKD, each patient must be assessed individually and there are insufficient data upon which to make a specific recommendation regarding potassium supplementation for cats with CKD. As potassium will shift in or out of cells based on changes in acid–base, it is critical to address acid–base status before assessing potassium status.

**Acid–Base Balance**

Metabolic acidosis is a common complication from CKD. In healthy animals, kidneys serve as the major homeostatic control point for maintaining acid–base balance. In response to acidosis, healthy kidneys increase net reabsorption of bicarbonate and increase secretion of hydrogen ions. In CKD, these homeostatic mechanisms fail, resulting in pronounced acidosis in 53% to 80% of cats with CKD. In addition, acidosis may cause or contribute to decreased renal function or progression of CKD either directly, or through potassium wasting. Healthy cats fed a low-potassium, acidifying diet developed negative potassium balance, metabolic acidosis and decreased renal function. Whether this was due to the potassium depletion or the acidosis could not be determined from that study.

Among the important adverse effects caused by acidosis are anorexia, nausea, vomiting, lethargy, weakness, and weight loss as well as increased protein catabolism, decreased protein synthesis, and loss of LBM, most of which may be improved by correction of acid–base balance. In human CKD patients, loss of muscle mass is linked with greater mortality. Glucocorticoids, insulin, insulinlike growth factor 1, and PTH all play important roles in the body’s response to acidosis, as reviewed by Franch. Release of calcium carbonate from bone to buffer the acid results in an increase in renal calcium excretion and negative calcium balance. Acidosis-induced activation of the ubiquitin–proteosome proteolytic system and branched-chain ketoacid dehydrogenase in muscle are part of the homeostatic mechanism that contribute to negative nitrogen balance and loss of muscle mass. Acidosis also seems to impair insulin signaling functions through its effect on phosphoinositide 3-kinase, resulting in increased protein degradation and loss of LBM. In healthy rats, induced acidosis resulted in a 70% increase in proteolysis and a 145% increase in amino acid oxidation. These changes would not only result in loss of LBM, but could generate more byproducts of protein oxidation including urea nitrogen and potential uremic toxins.

Increased intake of meat and animal proteins can contribute to acidosis, unless the diet has buffering agents added to counteract this. Commercial renal diets for cats and dogs typically are both protein restricted and have appropriate buffering agents as well as other nutrient modifications. This again raises the question as to whether protein restriction per se is actually beneficial in feline CKD, or if benefits attributed to protein restriction are actually due to other dietary factors including pH buffering.

Can simply correcting acid–base imbalance reduce or prevent the loss of LBM or slow the progression of CKD? Experimental evidence in rats suggests this to be true, but results vary depending on the experimental model. In human patients, retrospective studies have shown clear associations between acidosis and increased mortality in CKD. As cited in de Brito-Ashurst, several short-term trials in CKD patients receiving dialysis showed that correction of acidosis resulted in normalized protein catabolism and improved markers of nutritional status. A 2-year prospective, controlled clinical trial was conducted in nondialysis human CKD patients with both groups receiving the same standard care but 1 group also receiving bicarbonate supplementation. Of the 67 patients in the control group, 17 progressed to end-stage kidney disease, whereas only 9 patients in the bicarbonate group progressed to end-stage kidney disease.
renal failure within the first year compared with none in the treatment group. During the second year, creatinine clearance progressively deteriorated in the remaining patients in the control group but not in the treatment group. Additionally, the bicarbonate-treated group was able to consume more protein, showed an increase in normalized protein nitrogen appearance (a marker of nitrogen balance), and increased LBM as assessed by mid-arm muscle circumference.\textsuperscript{93} Even subtle differences in acid–base balance can influence protein balance. In a small cross-over study in human CKD patients undergoing peritoneal dialysis, adjusting the arterial pH to either the high normal (pH 7.44) or low normal (7.37) had a significant impact on net nitrogen balance, serum urea nitrogen, and total body protein synthesis.\textsuperscript{94}

At this time, no data in cats address the potential benefit of independently controlling acidosis on LBM, protein metabolism, or progression of CKD. However, clinical studies with “renal” diets designed with an alkalinizing effect as well as other nutrient modifications have shown positive benefits when fed to cats with CKD.\textsuperscript{29,31} It has been suggested that the need to provide therapy to maintain normal acid–base balance may increase if cats with CKD are fed protein-restricted diets,\textsuperscript{22} yet a comparative evaluation showed no incremental benefit of higher dietary base excess among commercial renal diets.\textsuperscript{29} Further research is needed to better define both the role of alkalinization and the optimum amount to address acid–base imbalance in CKD.

Although the evidence supports the need to correct metabolic acidosis in CKD cats, data on which to create specific treatment and monitoring parameters are lacking. Current IRIS guidelines suggest that blood bicarbonate or TCO\textsubscript{2} should be maintained in the range of 16 to 24 mmol/L once the patient is stabilized and hydrated. If needed, potassium citrate or sodium bicarbonate should be supplemented to effect.

**Energy Intake, Loss of Body Weight, and Body Condition**

Studies of healthy aging cats, identify a decline in feline digestive capability with increasing age.\textsuperscript{39,95,96} Both fat digestion and protein digestion tend to decrease in cats more than 12 years of age.\textsuperscript{39} Many otherwise healthy geriatric cats have increased requirements for calories and protein owing to digestive and metabolic inefficiencies.\textsuperscript{39,97–99} Maintaining weight and body condition in nonobese cats prolongs lifespan.\textsuperscript{41} Cats diagnosed with CKD may live for many years.\textsuperscript{8,10} Because most cats with CKS are older, these observations in healthy aging cats must be considered when considering dietary management for CKD patients.

Weight loss, with loss of muscle and LBM, is common among healthy aging cats.\textsuperscript{98} Sarcopenia, the age-associated loss of LBM, occurs slowly over many years. Insufficient dietary protein intake can exacerbate LBM loss, especially in aging cats.\textsuperscript{43} Loss of body weight also tends to occur slowly in geriatric cats unless associated with disease. Loss of body fat tends to occur much later in life, and is a predictor of mortality. Maintaining body weight and LBM seems to reduce the risk for morbidity and mortality in aging cats. Cachexia is the more aggressive loss of LBM and body mass that occurs secondary to disease, especially neoplasia, heart failure and kidney failure. Although dietary management alone cannot prevent or reverse sarcopenia or cachexia, inadequate calorie or protein intake can worsen it.\textsuperscript{43,100} In healthy adult cats, 32\% to 34\% of calories from protein seems to be adequate to maintain LBM.\textsuperscript{38,99} Limited research suggests that apparently healthy geriatric cats may need more than this, although no published studies have addressed this question in cats with CKD.\textsuperscript{43}

Thin body condition, as well as poor muscle condition and weight loss, are common in cats with CKD with 2 of the most consistent findings among cats with CKD being inappetance and weight loss.\textsuperscript{42,101–103} Weight loss usually begins before a diagnosis of CKD is made.\textsuperscript{39,102,104} Retrospective evaluation of the medical records of IRIS
staged CKD cats showed a weight loss of 8.9% in the 12 months before diagnosis of CKD but also showed that this weight loss began up to 3 years earlier. This is similar to the data reported by Perez-Camargo in colony cats. Among cats dying from CKD, median body weight loss began about 2.5 years before death, accelerating as the disease progressed. How much of that weight loss was related to the condition and how much related to diet composition or preference, nausea, inappetence, and other factors, is unknown and would be difficult to parse out. In 1 retrospective study, cats with body weights below the median (4.2 kg) at time of diagnosis of CKD had a significantly shorter survival time after diagnosis. In a different study, sustained weight loss occurred in at least 67% of cats with CKD. Those that lost weight had a median survival time of 401 days compared with 771 days for all cats. These data suggest that preventing or minimizing weight loss in CKD cats by improving palatability and ensuring adequate consumption of calories and protein might prolong lifespans.

In other species, loss of LBM in CKD patients is associated with increased morbidity and mortality. This loss seems to be due, at least in part, to inappropriately increased muscle protein catabolism coupled with reduced protein synthesis. Compared with healthy human patients, those with CKD had a 27% to 37% reduction in synthesis of muscle proteins. Even small but persistent imbalances between protein synthesis and degradation cause substantial protein loss over time. Although simply providing more dietary protein will not eliminate the CKD-stimulated protein loss, reducing protein intake may accelerate the loss.

Another important factor that may increase the loss of LBM is metabolic acidosis. Metabolic acidosis secondary to CKD results in loss of muscle protein predominantly through stimulation of catabolism. Buffering the diet to correct acidosis decreases the protein degradation, stimulates protein synthesis, and decreased loss of LBM. Increasing dietary protein intake may also aid in acid–base balance because protein provides the ammonia that allows for renal excretion of acidic hydrogen ions via ammonium. Finally, a critical factor influencing loss of body weight and LBM is calorie intake. Regardless of the macronutrient balance in the diet, inadequate calorie intake will contribute to loss of weight, LBM, and fat mass. Poor intake is a common finding reported in cats with CKD.

Exact energy requirements for patients with CKD cannot be calculated owing to considerable individual variability. The average geriatric cat requires more calories per unit body weight compared with middle aged cats, primarily owing to difficulties with digestion and metabolism. Approximately 33% of apparently healthy cats older than 12 have a reduced ability to digest fat and about 20% of cats older than 14 have trouble digesting protein. Cats with illness that may influence their metabolic efficiency, such as diabetes mellitus, hyperthyroidism, or CKD, will likely have further increases in needs. The most appropriate way to determine if an individual patient is consuming adequate calories is to track actual intake and weight changes: cats that are losing weight are not consuming enough calories.

Getting adequate calories into cats with reduced appetites can be difficult. This can be particularly difficult when attempting to feed a reduced protein food, because cats generally prefer higher protein diets. Several feeding management approaches to consider are listed in Table 2. To reduce the risk of development of a diet aversion, it is always preferred to stabilize and hydrate patients before introducing them to a new diet and to introduce it to them in a familiar environment, rather than in the hospital setting. If it is deemed appropriate to introduce a commercial renal diet, 1 option is to provide samples from several manufacturers, including both dry and wet foods, and allow the cat to select what it finds most palatable. Because most cats with CKD
are geriatric, many tips on feeding geriatric cats and providing an appropriate environment also would apply to CKD cats and may help with food intake.\textsuperscript{98,107,108} Appetite stimulants (eg, mirtazapine 2 mg orally every 48 hours) can be used as a short-term adjunct to feeding management.\textsuperscript{109} As with all cats, it is important to monitor food intake and changes in body weight so that necessary adjustments can be made. If intake remains poor, feeding tubes should be strongly considered.

Water

In healthy cats with access to water, drinking increases or decreases as needed to maintain hydration. Drinking water intake ranges from about 100 to 150 mL per cat per day when cats eat dry food to as little as 5 mL/kg per day\textsuperscript{110} or even no water at all with very high moisture diets.\textsuperscript{111–113} Cats with CKD will often consume considerably more water than healthy cats but, owing to excess losses, may become dehydrated.

Water is essential to perfuse tissues with oxygen and nutrient carrying and waste scavenging mechanisms. Dehydration may contribute to renal ischemia and deterioration of kidney function by compromising renal blood flow. The clinical consequences of dehydration include all of the manifestations of uremia owing to concentration of

<table>
<thead>
<tr>
<th>Table 2</th>
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<tbody>
<tr>
<td>Feeding management recommendations to increase calorie intake in cats with CKD</td>
</tr>
<tr>
<td>Stabilize patient before introducing a new diet. Introducing a new diet while the patient is feeling ill or is stressed from being hospitalized, there is a greater likelihood that an aversion to the food will form and the food will be rejected.</td>
</tr>
<tr>
<td>Introduce any new food gradually Each day, provide the cat with the new food in its old bowl and the old food in a new bowl. Once the new food is being at least partly consumed, gradually decrease the amount of the old food and increase the amount of the new food offered. Transitions can occur in as little as 1 wk, or take up to a month.</td>
</tr>
<tr>
<td>Provide a choice of wet and dry foods Some cats have an aversion to either dry or wet food, so should receive the type of food they prefer.</td>
</tr>
<tr>
<td>Provide a choice of foods from different manufacturers Although all pet food companies strive to make their foods palatable, individual cats may choose those from 1 maker over another. This is also an approach to consider if a patient stops eating 1 brand and seeks variety.</td>
</tr>
<tr>
<td>Consider access to the bowl Many cats with chronic kidney disease have concurrent osteoarthritis. Raising the food and water bowls several inches can make eating and drinking less painful. If food bowls are on raised surfaces, consider providing ramps or other access aids. Wider lower bowls that don't interfere with whiskers may also be considered.</td>
</tr>
<tr>
<td>Offer palatable foods If a patient refuses all options of the veterinary preferred diet, offer foods that the cat prefers and manage the disease via pharmaceutical options</td>
</tr>
<tr>
<td>Appetite stimulants and feeding tubes Appetite stimulants (eg, cyproheptadine 1 mg orally every 12 h, mirtazapine 2 mg orally every 48 h) can be used very short term, but should not be relied on for long-term management. If voluntary intake is inadequate, placement of a permanent, large-bore feeding tube should be strongly considered.</td>
</tr>
</tbody>
</table>
uremic toxins, as well as constipation. Rehydration aids in acid–base and electrolyte homeostasis and dilutes uremic toxins. The most physiologic route to maintain hydration is through increasing water ingestion. Adding water to the food, offering flavored liquids, installing a pet fountain, and ensuring that the water is fresh may make other methods unnecessary. Dividing the daily energy requirement into multiple small meals was shown to result in increased water intake in healthy cats in 1 study,114 and ad libitum feeding was associated with significantly greater water intake in a different study.115 Feeding canned foods may aid with hydration. Cats eating 100% wet food consumed twice as much water than when they ate dry only, retained more water suggesting improved hydration, and had larger volumes and less concentrated urine.111–113,116 Therefore, when acceptable to both owner and cat, feeding canned food may be preferred for cats with CKD.

Controlled, randomized studies assessing the efficacy of fluid therapy in the treatment and ongoing management of CKD in cats are lacking. However, with an impaired ability to concentrate urine, despite polydipsia, exogenous fluids are required both to correct dehydration as well as to maintain hydration and euvolemia in IRIS stages 3 and 4 as well as in acute on chronic crises. Discussion of types of fluids, routes, amounts, and frequency of administration is beyond the scope of this nutrition article.

Other Nutrients

Consistent with studies in human patients, several studies have identified increased oxidative stress in cats with CKD.6,117–119 Recent evidence suggests that oxidative stress may play a key role in fibrosis development,120 a very common finding in feline CKD. The finding of oxidative stress is not unto itself a surprising finding, but does raise the question of how, and if, it should be addressed. In a small nonrandomized, controlled study, cats with IRIS stage 2 or greater were fed a dry diet supplemented with vitamins E and C and beta-carotene. Markers for DNA damage were reduced compared with the preceding period during which they were fed a nonsupplemented diet, suggesting that the antioxidants reduced oxidative stress in these cats.117 Unfortunately, the study was not designed to identify specific antioxidants or dosages of antioxidants that might be effective in controlling oxidative stress in CKD, so additional research is warranted.

COMMENTARY: FUTURE DIRECTIONS

Dietary protein is not toxic to kidneys. Creatinine and urea, whether generated through the catabolism of exogenous or endogenous protein, are 2 of a long list of purported uremic toxins (Table 3). A review of the effects of uremic toxins on multiple organ systems in humans with CKD and acute kidney injury concludes that neither creatinine nor urea concentrations reflect GFR or toxicity owing to the presence and interactions of many other endogenous metabolites.121 No single uremic toxin accounts for the clinical spectrum of uremia. Instead, uremia results from the interactions of inflammation, malnutrition, hypoalbuminemia, increased concentrations of protein-bound solutes as well as generation of nonnutritional toxins.122–124

Although uremic toxins can result in malnutrition, malnutrition itself results in inflammation, morbidity, and mortality in human patients with CKD.123 Possible explanations include that (a) not all protein and nutritional degradation metabolites are toxic, (b) hypoalbuminemia enhances protein-bound toxin availability, (c) tissue catabolism results in generation of more toxic solutes than those from protein metabolism, (d) compounds unrelated to protein degradation contribute to inflammation and malnutrition, and (e) renal clearance is required for removal of nonprotein derived toxins.
Despite numerous experimental studies and clinical trials having been performed, questions about feeding and managing the cat with CKD remain. Some of these include the following.

1. Do we rely too much on diet? Are there other approaches we could use to reduce uremic toxin production or absorption? Renal diets were developed at a time when there were no effective medications for CKD. Now, the availability of phosphorus binders, potassium gluconate or citrate, omega-3 fatty acids, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and amlodipine provide greater ability to address the specific needs of the individual patient without inducing malnutrition.

2. Do different types of kidney disease require different dietary therapies? Fibrosis associated with interstitial changes is the endpoint for most cats; however, what etiology initiates the process is generally unknown in an individual cat.

3. At what point in disease progression should dietary therapy be implemented, if at all? In theory, would it be better to address acid–base balance initially, and then phosphorus binding, or vice versa?

4. What is the optimal amount of protein for cats with CKD? How much restriction, if any, is necessary? Interestingly, the benefits of protein restriction in human CKD remains an area of controversy with metaanalyses failing to show clear advantages\(^\text{125–127}\). Similar to cats, protein malnutrition, sarcopenia, and iron deficiency are clinical problems in human CKD patients following low protein regimes. A prospective study in human CKD patients contrasting protein and phosphorus restriction concluded that the risks associated with protein restriction may

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**Table 3**

**List of purported uremic toxins**

<table>
<thead>
<tr>
<th>Small Water Soluble Solutes</th>
<th>Protein-bound Solutes</th>
<th>Middle Molecules</th>
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<tbody>
<tr>
<td>Asymmetric dimethylarginine</td>
<td>3-Deoxyglucosone</td>
<td>Adrenomedullin</td>
</tr>
<tr>
<td>Benzylalcohol</td>
<td>CMPF</td>
<td>Atrial natriuretic peptide</td>
</tr>
<tr>
<td>(\beta)-Guanidinopropionic acid</td>
<td>Fructoselysine</td>
<td>(\beta_2)-Microglobulin</td>
</tr>
<tr>
<td>(\beta)-Lipotropin</td>
<td>Glyoxal</td>
<td>(\beta)-Endorphin</td>
</tr>
<tr>
<td>Creatinine</td>
<td>Hippuric acid</td>
<td>Cholecystokinin</td>
</tr>
<tr>
<td>Cytidine</td>
<td>Homocysteine</td>
<td>Clara cell protein</td>
</tr>
<tr>
<td>Guanidine</td>
<td>Hydroquinone</td>
<td>Complement factor D</td>
</tr>
<tr>
<td>Guanidinocacetic acid</td>
<td>Indole-3-acetic acid</td>
<td>Cystatin C</td>
</tr>
<tr>
<td>Guaninosuccinimic acid</td>
<td>Indoxyl sulfate</td>
<td>Degranulation inhibiting protein I</td>
</tr>
<tr>
<td>Hypoxanthine</td>
<td>Kinurenine</td>
<td>Delta-sleep–inducing peptide</td>
</tr>
<tr>
<td>Malondialdehyde</td>
<td>Kynurenic acid</td>
<td>Endothelin</td>
</tr>
<tr>
<td>Methylguanidin</td>
<td>Methylglyoxal</td>
<td>Hyaluronic acid</td>
</tr>
<tr>
<td>Myo-inositol</td>
<td>N-carboxymethyllysine</td>
<td>Interleukin 1(\beta)</td>
</tr>
<tr>
<td>Orotic acid</td>
<td>P-cresol</td>
<td>Interleukin 6(\beta)</td>
</tr>
<tr>
<td>Orotidine</td>
<td>Pentosidine</td>
<td>Kappa-lg light chain</td>
</tr>
<tr>
<td>Oxalate</td>
<td>Phenol</td>
<td>Lambda-lg light chain</td>
</tr>
<tr>
<td>Pseudouridine</td>
<td>P-OH hippuric acid</td>
<td>Leptin</td>
</tr>
<tr>
<td>Symmetric dimethylarginine</td>
<td>Quinolinic acid</td>
<td>Methionine-enkephalin</td>
</tr>
<tr>
<td>Urea</td>
<td>Spermidine</td>
<td>Neuropeptide Y</td>
</tr>
<tr>
<td>Uric acid</td>
<td>Spermine</td>
<td>Parathyroid hormone</td>
</tr>
<tr>
<td>Xanthine</td>
<td></td>
<td>Retinol binding protein</td>
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<tr>
<td></td>
<td></td>
<td>Tumor necrosis factor alpha</td>
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</table>

Abbreviation: CMPF, carboxy-methyl-propyl-furanpropionic acid.

outweigh the benefits from phosphorus restriction, and suggested that protein restriction as a means to control phosphorus intake is not justified. Kasiske and associates conclude that the relatively weak effect on progression of renal disease provided by dietary protein restriction in human CKD suggests that better therapies are needed.

5. Does the type of protein, or the amino acid composition of the protein, make a difference in cats? There is evidence in humans and rats that types of protein can differentially influence the effect of protein on GFR, acid–base and other effects. This effect was not observed in dogs and no data are available for cats.

6. Will a cat in IRIS stage 3 or 4 benefit adequately if phosphorus is restricted by means other than diet? No controlled clinical trials address this question. One study using a remnant kidney model demonstrated persistent benefit of a chitosan calcium carbonate phosphorus binder when stage 1 and 2 cats were fed a maintenance diet.

7. Might some cats with advanced disease benefit from increased dietary protein levels? As discussed, regular reassessment of the patient enables evaluation of muscle and body condition, which is helpful in changing dietary treatment recommendations if warranted. As loss of LBM is detrimental as well as predictive of progression, increasing dietary protein and using alternate methods to restrict phosphorus or uremic toxins should be considered. When patients fail to eat adequate calories (protein, fat, or carbohydrate), then feeding support is required. Would a more palatable diet help? Evidence-based guidelines for type of assistance and timing would be helpful.

8. Do we rely too heavily on creatinine as a measure of azotemia? What are the actual uremic toxins that cause adverse effects in cats and what can we do about them? This remains an area of potential research.

9. Should we be investigating phosphatonins (eg, FGF-23) and their role in phosphate homeostasis in cats and potentially seeking ways to block or correct FGF-23 as GFR declines? Finch and colleagues reported an inverse relationship between FGF-23 concentrations and GFR and demonstrated that FGF-23 is increased in cats that go on to become azotaemic before phosphate concentrations increase. PTH also changes before serum phosphorus. Would these be better markers of progression of renal dysfunction?

10. Progression of renal fibrosis is thought to be related to the ongoing production of proinflammatory and profibrotic cytokines. Proteinuria, hypoxia, hyperphosphatemia, ageing, and chronic inflammation have been investigated and are believed to maintain this state. Should the focus of early identification (eg, symmetric dimethylarginine) and treatment be modification of the inflammatory mediators?

11. Is it appropriate to restrict protein in cats with proteinuria? Although protein in the urine may initiate an inflammatory response that ultimately progresses to interstitial fibrosis, muscle wasting and a perceived decreased quality of life may result in an earlier death, either owing to general decline in health or earlier requested euthanasia. Would this be better addressed pharmacologically rather than risking malnutrition? Malnutrition also results in inflammation and mortality; therefore, preventing malnutrition (as well as sarcopenia), is critically important when managing the feline CKD patient.

SUMMARY

As stated, we agree that (1) abnormalities in normal homeostasis produced by renal insufficiency are influenced by dietary intake, (2) the kidney is susceptible to
Table 4
Summary of evidence supporting nutrient modification in cats with chronic kidney disease

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Documentation for Benefit to Change</th>
<th>Evidence-based Target for Dietary Intake</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein</td>
<td>Conflicting results in remnant kidney model; no data testing protein restriction independent of other nutrients in spontaneous CKD cats</td>
<td>Restriction not supported; recommended target: 30%–40% of calories from protein</td>
<td>Commercial renal diets provide as little as 20% of calories from protein.</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>0.42% superior to 1.56% (dry basis) in remnant kidney cats; no data testing phosphorus restriction independent of other nutrients in spontaneous CKD cats</td>
<td>Some restriction is supported, but inadequate data on which to base a dietary target</td>
<td>IRIS guidelines suggest maintaining serum phosphorus in the low normal range. PTH and FGF-23 may be elevated even with normal serum phosphorus</td>
</tr>
<tr>
<td>Sodium</td>
<td>Conflicting data on adverse effects at 1.2% dietary sodium (dry basis); adverse effects from too little sodium noted in remnant kidney models at about 0.33% sodium, dry basis</td>
<td>Restriction is contraindicated; avoid sodium levels &gt;1.0% of diet dry matter</td>
<td>Commercial renal diets may contain insufficient sodium and stimulate the RAAS system; if low-sodium diet is fed, consider potassium supplementation</td>
</tr>
<tr>
<td>Potassium</td>
<td>Hypokalemia is associated with renal dysfunction but no benefit documented in eukalemic CKD cats</td>
<td>Treat hypokalemic cats as needed to maintain serum potassium within the normal range</td>
<td>Correct acid–base imbalance before testing potassium</td>
</tr>
<tr>
<td>Omega-3 fatty acids</td>
<td>15% dietary omega-3 fatty acids affect GFR and renal blood flow; no data to support long-term benefit from supplementation</td>
<td>No data in cats with CKD</td>
<td>Long-chain n-3 fatty acids, especially EPA, reduce inflammation, blood pressure and proteinuria in other species</td>
</tr>
<tr>
<td>Alkalization</td>
<td>No studies in cats have evaluated bicarbonate supplementation alone</td>
<td>No data in cats with CKD</td>
<td>IRIS guidelines suggest maintaining normal TCO2 levels</td>
</tr>
<tr>
<td>Calories</td>
<td>No studies in cats have evaluated calorie supplementation alone</td>
<td>Maintain calorie intake sufficient to support ideal body condition</td>
<td>Individual calorie needs vary greatly but are typically increased in aged cats</td>
</tr>
<tr>
<td>Water</td>
<td>No studies in cats have evaluated hydration alone</td>
<td>No data in cats with CKD; healthy cats need about 50 mL water/kg body weight</td>
<td>Rehydration as needed aids in acid–base and electrolyte homeostasis and dilutes uremic toxins</td>
</tr>
</tbody>
</table>

Abbreviations: CKD, chronic kidney disease; FGF-23, fibroblast growth factor-23; GFR, glomerular filtration rate; IRIS, International Renal Interest Society; PTH, parathyroid hormone; RAAS, renin-angiotensin-aldosterone system.

Given the smaller number and size of the studies in veterinary medicine, we are unable to perform metaanalysis, thus it seems prudent to make the following recommendation: when prescribing restricted protein renal diets practitioners must carefully monitor their patients’ protein and energy intake and nutritional status, as evidenced by body and muscle condition as well as enjoyment of meals/quality of life. If deterioration in any of these is noted with no other apparent reason, alternate diets or means to reduce phosphorus should be considered.
self-perpetuating injury, which may be influenced by dietary modification, and (3) the responses of cats with CKD to dietary or pharmaceutical management will vary dramatically, making individualized therapy with appropriate follow-up necessary.\textsuperscript{76} Although clinical studies have shown a benefit from feeding commercial renal diets compared with maintenance diets for cats with CKD, numerous nutrients differed in each study and it is not clear that all nutrient modifications are necessary. As is the case throughout veterinary medical research, we lack statistical power owing to small studies, small numbers of studies, and lack of confirming or refuting studies, and are therefore left to draw conclusions based on very limited data. The sum of the evidence (Table 4) suggests that addressing the dysregulation of phosphorus that occurs in CKD is of value. Whether this is best done through phosphorus-restricted diets or the addition of phosphate binders remains to be determined. Evidence regarding a beneficial effect in CKD from dietary protein restriction is lacking, as is evidence to support sodium restriction. Evidence in other species suggests a benefit for addressing acid–base imbalances and there is evidence to support potassium supplementation when potassium depletion is detected. Limited evidence suggests a potential benefit from long-chain omega-3 fatty acid supplementation. Finally, it should be noted that dietary management of CKD is no longer the only option. Appropriate medical management, for example, phosphate binders, alkalining agents, angiotensin-converting enzyme inhibitors, and so on, may preclude the need for special diets.

REFERENCES


125. Levey AS, Greene T, Beck GJ, et al. Dietary protein restriction and the progression of chronic renal disease: what have all of the results of the MDRD study


