

## Nutritional management of early CKD: IRIS Stage 1 and 2



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Nutrition is arguably the most important aspect of chronic kidney disease (CKD) management. By manipulating the composition of a patient's diet, we can reduce the accumulation of metabolic waste products and minimize the self-perpetuating cycle of glomerulotubular damage. Because CKD encompasses a wide spectrum of pathology and severity, nutritional goals will also vary by stage of disease and underlying etiology (if known). Most therapeutic diets designed for CKD utilize a combination of moderately restricted protein, phosphorus, and sodium with moderately elevated concentrations of omega-3 fatty acids and potassium (Table 1). The use of symmetric dimethylarginine (SDMA) and ultrasound are allowing earlier detection of CKD, yet little is known about the optimal nutritional plan for animals in the IRIS stage 1 and 2 categories of CKD.<sup>1,2</sup> The degree to which the nutrients should be modified from traditional diets in patients with early CKD is not well understood, and a balance must be struck between protecting the kidneys from further damage while maintaining diet palatability and body musculature.

### Protein

When assessing the protein content of a diet, it is important to remember that animals actually require amino acids, rather than protein. By feeding protein sources with well-balanced ratios of essential amino acids that are readily digested and absorbed, we can lower the overall protein content of the diet while preventing protein malnutrition. It is also important to note that all diets currently marketed for management of CKD in dogs and cats exceed the recommended protein allowance set by the National Research Council.<sup>3</sup> The goals behind lowering the concentration of protein in diets fed to dogs and cats with CKD are to reduce the amount of nitrogenous waste products produced during cellular metabolism, while also minimizing the amount of protein entering the glomerular filtrate of the kidneys. The restriction of protein

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as a dietary management strategy for CKD has become increasingly controversial. Some argue dogs and cats with kidney disease should not

be placed on a low protein diet in an effort to retain muscle mass and increase diet palatability while others cite research suggesting restricted protein diets in combination with other nutrient modifications reduce morbidity and prolong lifespan.<sup>4-7</sup>

### Cats

Cats are obligate carnivores with higher dietary protein requirements compared to dogs.<sup>3</sup> When fed inadequate amounts of protein, cats will catabolize muscle and other lean tissue to fulfill their metabolic needs, resulting in a gradual loss of lean body mass (LBM). A study evaluating varying levels of dietary protein in 20 neutered male cats over a 2 month period found cats fed 73 grams and 56 grams of protein per 1000kcal lost lean muscle mass while those fed 95 grams per 1000kcal maintained their lean mass.<sup>8</sup> While the results of this study are intriguing, there are a couple of limitations to consider. First, cats in the moderate protein group had lower energy intake compared to the other groups. When placed in a negative energy balance, endogenous protein is utilized for energy and this may have resulted in lower muscle mass in this group compared. Second, the sample size of the study was small with only 4 cats in the low protein group undergoing body composition analysis. Only a handful of research abstracts have evaluated lean body mass in cats with CKD. In a small study of 7 cats with early CKD (creatinine ranging from 1.6-2.1 mg/dl), serum albumin and lean body mass were maintained after 30 weeks consuming a diet with 65.3 grams of protein per 1000kcal.<sup>9</sup> Another study of 10 cats with spontaneous CKD (staging not provided) rotated diets with 16% metabolizable energy (ME), 20% ME, and 24% ME from protein (45g, 57g, 68g of protein per 1000kcal based on 3.5 kcal/g conversion factor)

**Table 1:** Nutrient profile of typical therapeutic diets designed for CKD management in dogs and cats

Nutrient (g/1000kcal)	Therapeutic CKD diets	Hill's k/d Early Stage†	AAFCO*	FEDIAF**	NRC recommended allowance for adult dogs <sup>3</sup>
Protein	31-41	42	45	45	25
Fat	40-62	47	14	13.75	14
Phosphorus	0.5-0.8	0.8	1.0	1.0	0.75
Potassium	1.1-2.3	1.7	1.5	1.25	1.0
Sodium	0.4-1.2	0.42	0.2	0.25	0.2
EPA + DHA	0.4-1.2	1.27	n/a	n/a	0.1

Nutrient (g/1000kcal)	Therapeutic CKD diets	Hill's k/d Early Stage†	Purina NF Early Care	AAFCO*	FEDIAF**	NRC recommended allowance for adult cats <sup>3</sup>
Protein	58-76	77	90	65	62.5	50
Fat	42-63	53	35.1	22.5	22.5	22.5
Phosphorus	0.8-1.2	1.1	0.9	1.25	1.25	0.64
Potassium	1.9-3.5	2.3	3.5	1.5	1.5	1.3
Sodium	0.5-1.0	0.6	0.7	0.5	0.19	0.18
EPA + DHA	1-1.2	1.05	1.2	n/a	n/a	n/a

\*2017 AAFCO Adult Maintenance Minimum

\*\* 2017 FEDIAF Adult Minimum Recommended Level

† European formula

for 4 months intervals. The 45g protein diet resulted in lower hematocrit, weight loss despite higher calorie intake, and lower lean body mass compared to the 68 grams per 1000kcal diet. The low protein diet also resulted in lower albumin and weight loss compared to both the medium and high protein diets. These results suggest dietary protein levels close to 68 grams of protein per 1000kcal are superior to lower protein diets for cats with CKD.<sup>10</sup>

Protein restriction for managing feline CKD has been a mainstay of therapy for more than 40 years.<sup>11</sup> Several studies show diets designed for CKD with restricted concentrations of phosphorus and protein increase survival in cats with IRIS stage 2 CKD and greater.<sup>6,7,12</sup> Two of the studies utilized diets that also had increased omega-3 fatty acids and lower sodium concentrations.<sup>6,12</sup> Based on these studies, there is strong evidence to support the use of therapeutic renal diets to reduce clinical signs of uremia and prolong survival in cats with advanced kidney disease. A more recent study evaluated a therapeutic renal diet in cats with early stages of renal disease (IRIS Stage 1 and 2) and found no change in body weight, BUN, creatinine, urine protein:creatinine ratio (UPC), or urine specific gravity over a 12 month period.<sup>13</sup> Since there was no control diet in the study, it is difficult to determine if stability in renal parameters was due to the diet, or just slow disease progression in early CKD. In addition, muscle condition was not assessed in the study, so it is difficult to determine if protein levels were adequate to sustain muscle mass.

Some information regarding the impact of protein in feline CKD can be gleaned from studies using five-sixth nephrectomy models. In one such study, cats with CKD fed a high protein diet (approximately 130 g/1000kcal) for twelve months maintained body weight while those fed a low protein (approximately 70 g/1000kcal) diet lost weight, despite similar calorie intake.<sup>14</sup> Protein intake also did not affect tubular lesion, cellular infiltrate, or fibrosis on renal histopathology. Similarly, higher protein intake did not affect GFR or UPC.<sup>14</sup> A similar study also using a five-sixth nephrectomy model found cats fed a high protein diet (approximately 108 g/1000kcal) had significantly lower

serum creatinine, higher inulin clearance, and maintained body weight better than cats fed a diet with about 58 grams of protein per 1000kcal.<sup>15</sup> However, the cats on the high protein diet had higher serum urea nitrogen and developed more renal pathology. Unfortunately, there were significant limitations to this study, namely, the higher protein diet was deficient in potassium and clinical signs of hypokalemia developed in more than one-half of the cats fed this diet. In cats with naturally occurring renal disease, restriction of protein in combination with other dietary modifications appears beneficial, particularly in later stages of disease. However, more research is needed to determine if protein restriction is harmful or helpful for cats in early stages of CKD.

### Dogs

Most studies evaluating protein restriction in dogs with CKD are based on the remnant kidney model instead of naturally occurring disease. Moderate protein and phosphorus restriction (35 g and 750 mg per 1000kcal, respectively) reduced morbidity and mortality in Beagles with induced CKD, while high protein intake (110 g/1000kcal) worsened clinical signs and increased death rates.<sup>4</sup> Low protein diets containing 17 g/1000kcal lowered plasma protein and albumin concentrations.<sup>4,5</sup> Unfortunately, it is difficult to determine the true impact of dietary protein in these studies as the diets varied in caloric density, phosphorus, sodium, and protein digestibility. Finco, et al also utilized dogs with nephrectomy-induced CKD. When dogs were fed low and high protein diets (approximately 35 versus 72 g/1000kcal based on a 4000 kcal/kg DMB) for 2 years, they found dietary protein content did not affect survival or UPC. Higher protein diets did lead to higher BUN, but lower creatinine concentrations.<sup>14</sup>

While there is little information regarding the role of dietary protein in early stages of CKD, a couple of recent studies have tested therapeutic renal diets in IRIS stage 1 CKD. One study evaluated a renal therapeutic diet (35 g/1000kcal) in nine dogs with early renal disease (SDMA  $\geq$ 14  $\mu$ g/d and creatinine < 2.0 mg/dl) and found no change in albumin, but lower concentration of BUN, creatinine, and SDMA

after 6 months.<sup>15</sup> The same group then expanded the initial report to include a total of 20 IRIS stage I CKD dogs and had similar findings.<sup>16</sup> The decreased creatinine concentrations found in these studies could indicate either increased renal clearance, or reflect muscle mass reduction.<sup>17</sup>

*Therapeutic renal diet fed to dogs with IRIS Stage 1 CKD resulted in stable albumin and lower sCr, BUN, and SDMA in 6 months.*

### Proteinuria

Based on the intact nephron hypothesis, once a critical mass of nephrons is reached, remaining nephrons hypertrophy and signal the need for increased blood flow, glomerular filtration rate, and pressure. The chemical and electrical selective barriers of the glomeruli are impaired and increased levels of protein pass into the filtrate. Eventually the tubular reabsorption of protein is overwhelmed and tubular cells begin to secrete inflammatory mediators that further damage the kidneys.<sup>18</sup>

Protein restricted diets have been shown to reduce glomerular damage and urinary protein concentrations in dogs with hereditary nephritis.<sup>19,20</sup> The degree of protein restriction needed to mitigate renal damage secondary to proteinuria in dogs is unclear. For example, when dogs with nephritis ate diets containing 72 or 33 grams of protein per 1000 kcal, mean UPC were 4.7 and 1.8, respectively. However, dogs on the lower protein diet also had reductions in albumin and body weight.<sup>20</sup> A more recent study evaluated a renal diet in combination with ACE-inhibitors in proteinuric CKD dogs and saw no change in albumin or body condition score over a 5-month period.<sup>21</sup> Proteinuria associated with CKD is less common in cats, but a high-protein intake may contribute to the development of glomerular lesions and promote proteinuria in this species.<sup>13,22</sup> Careful consideration of dietary protein intake is required in dogs and cats with proteinuria and current protein intake should be considered. For example, a proteinuric dog currently eating a high protein diet may see substantial improvement by reducing his dietary protein intake by 25 to 50%. Careful monitoring and assessment of other clinical signs are needed to balance protein losses and renal damage in these patients.

*Restriction of dietary protein intake should always be considered in proteinuric dogs and cats.*

### Phosphorus

While there is still much to learn regarding the need and extent of protein restriction that is optimal for cats and dogs with early CKD, the need for phosphorus restriction is less controversial. As the kidney retains phosphorus, the parathyroid gland is stimulated to release PTH to increase phosphorus excretion by the kidney. However, PTH also stimulates the release of phosphorus from the bone, which exacerbates hyperphosphatemia. In addition, calcitriol deficiency occurs secondary to decreased renal production of 1- $\alpha$ -hydroxylase and hyperphosphatemia. This ultimately leads to calcium deficiency and increased PTH production. Studies have shown that by reducing phosphorus in the diet, we can reduce hyperphosphatemia and the sequela of renal secondary hyperparathyroidism.<sup>14,23</sup>

The importance of phosphorus restriction was demonstrated by a study in which 24 dogs with induced kidney disease were fed a diet with 32% protein dry matter with and without phosphorus restriction, over a 2 year period. Dogs on the high phosphorus diet had lower survival rates (33%) compared to the restricted phosphorus

group (75%).<sup>14</sup> In a study by Ross and colleagues, cats with induced kidney disease fed a low phosphorus diet (approximately 0.6 g/1000kcal based on a 4000 kcal/kg DMB) had mild to no renal histologic changes while those on a high phosphorus diet (approximately 3.9 g/1000)

had renal mineralization, fibrosis, and mononuclear cell infiltrates.<sup>23</sup> While there are no studies specifically evaluating the impact of phosphorus restriction in dogs and cats with early stages of CKD, it is generally accepted that lower dietary phosphorus is unlikely to have significant negative consequences. In addition, the IRIS currently recommends feeding a phosphorus-restricted diet even in early stages of CKD to maintain plasma phosphorus below 4.6 mg/dL.

### Other nutrients

Other nutrients to consider with renal disease are sodium, potassium, and omega-3 fatty acids. Sodium restriction has been recommended as a method of combatting hypertension associated with CKD. However, studies demonstrating that sodium reduction improves hypertension are lacking in dogs. A study by Kirk et al demonstrated (2.94 g Na/1000kcal) lead to increases in BUN, phosphorus, and creatinine in cats with various stages of CKD.<sup>24</sup> Interestingly, blood pressure was not significantly affected. Hypokalemia is a well-recognized consequence of renal disease in dogs and cats and most prescription renal diets have moderately high levels of potassium. Though more common with acute kidney injury, some dogs with CKD can become hyperkalemic and may need a specially formulated potassium restricted homemade kidney diet.<sup>25</sup>

Omega-3 fatty acids in the form of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) competitively inhibit the formation of pro-inflammatory leukotrienes and prostaglandins from omega-6 fatty acids. Diets high in omega-3 fatty acids have been shown to reduce glomerular capillary pressure, proteinuria, and abate the decline of GFR in dogs with experimentally induced CKD.<sup>26</sup> A retrospective study by Plantinga et al. found cats fed a therapeutic kidney diet with a higher concentration of EPA had longer survival times compared to cats eating other therapeutic kidney diets.<sup>27</sup> A dosage of 40 mg/kg body weight EPA combined with 25 mg/kg body weight DHA per day has been recommended for dogs and cats with CKD.<sup>29</sup> This equates to approximately 1 gram of EPA and DHA per 1000 kcal of diet when fed at a 1.4 times resting energy requirements for adult maintenance. Some foods are supplemented with high concentrations of the omega 3 fatty acid alpha-linolenic acid (ALA). While this is an essential fatty acid for dogs and cats, the conversion of ALA to EPA and DHA is poor and consideration of omega 3 fatty acid doses should not be based on ALA concentrations.

### Summary

There is still much to learn about the nutritional needs of dogs and cats with IRIS stage 1 and 2 CKD. While the combination of moderately low protein, low phosphorus, moderate sodium, and moderately high potassium and EPA/DHA is proven to reduce uremia and extend the lifespan of dogs and cats with later stages of CKD, controversy remains regarding the optimal dietary protein concentrations for

early stages of this disease. Dogs and cats with early stages of CKD will likely tolerate higher concentrations of protein as compared to those with severe azotemia. With the advent of new therapeutic renal diets targeted to early stages of

CKD, it is reasonable, and likely advantageous, to feed a diet incorporating the principles of traditional renal diets while also providing higher concentrations of protein.

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