SUMMARY AND CLINICAL RELEVANCE

The effects of therapeutic renal foods on several clinical outcomes in pets with naturally occurring CKD have been studied at a number of 'Evidence Based Medicine' grade levels, with the studies published by Ross (Hill's[®] Prescription Diet[®] k/d[®] Feline vs. a control food) and Jacob (Hill's[®] Prescription Diet[®] k/d[®] Feline vs. a control food). Recent Hill's developments — an enhanced essential amino acid profile, high levels of carnitine and omega-3 fatty acids from fish oil, and the addition of E.A.T.™ Technology — provide benefits to these already proven foods. These enhancements to k/d[®] support the CKD patient's natural ability to maintain LBM and help ensure successful transitions of patients to this renal food which has been shown to decrease CKD-related deaths and improve quality of life.

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FOOTNOTES

^aRoyal Canin Veterinary Diet[®] Renal Support A Feline Dry, Royal Canin Veterinary Diet® Renal Support F Feline Dry and Royal Canin Veterinary Diet® Renal Support S Feline Dry.

¹¹ Data on file. Hill's Pet Nutrition Inc.

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Clinical Overview

New Solutions for Pets with Kidney Disease

NUTRITIONAL MANAGEMENT OF CHRONIC KIDNEY DISEASE

Key Points:

- Chronic kidney disease (CKD) is often seen in pets and is a major cause of morbidity and mortality.
- Renal therapeutic foods are the cornerstone of CKD management. Hill's[®] Prescription Diet[®] k/d[®] Canine and Feline are supported by randomized, controlled, clinical trials (grade I evidence).
- Pets with CKD also frequently suffer from cachexia, muscle loss due to chronic disease, and decreased appetite, both of which may impact their quality and quantity of life.
- Many pets with CKD are geriatric and they may also suffer from sarcopenia, the age-related loss of lean body mass (LBM). Sarcopenia may further perpetuate muscle loss in geriatric pets with CKD.
- k/d[®] is the first renal therapeutic food to contain targeted amounts of carnitine, omega-3 fatty acids and essential amino acids to help minimize loss of LBM associated with CKD. Additionally, k/d[®] dry contains breakthrough advancements in taste to further increase food and calorie intake in pets with CKD.

BACKGROUND

Chronic kidney disease is a major cause of morbidity and mortality in pets.¹ Nutritional management has been the cornerstone of longterm management of this condition in dogs and cats for many years and has been shown to significantly increase quality of life and survival.^{2,3} In fact, there is strong evidence behind nutritional management of canine and feline CKD with Hill's® Prescription Diet[®] k/d^{®,4,5}

Although nutritional management of CKD has been demonstrated to both prolong survival and improve quality of life in dogs and cats with CKD, changes in LBM and appetite further hamper quality of life in some patients. Over the past several years there has been growing acceptance within the veterinary community that poor appetite resulting in inadequate calorie and protein intake contributes to the morbidity of the disease. The following reviews the evidence for k/d° as well as the basis for the recent updates to the food.

DECREASED CKD-RELATED DEATHS, IMPROVED QUALITY OF LIFE

The only peer-reviewed, double-blinded, randomized and controlled study (grade I evidence) investigating the effects of a renal therapeutic food (Prescription Diet[®] k/d^{e} Feline) on renal-related mortality in cats was published

by Ross and colleagues in 2006.³ The control food was designed to mimic a typical feline maintenance food. The test food contained controlled phosphorus, protein and sodium and was non-acidifying. Cats with IRIS stage 2-4 CKD were randomly assigned to either the test (n=22) or the control (n=23) groups. This 2-year-long study showed that there were significantly fewer episodes of uremic crises in cats fed the renal food compared with the control food (P=0.02). Moreover, there were significantly fewer CKDrelated deaths of cats in the renal food group compared with cats fed the maintenance food (P=0.03).

Similarly, Prescription Diet[®] k/d[®] Canine is the only food supported by a peer-reviewed, double-blinded, randomized, controlled study to significantly reduce the number of uremic episodes and renal-related mortality when fed to dogs with naturally occurring CKD for 2 years.² In this study, 38 dogs with spontaneous CKD were randomized to either the control food (n=17) designed to mimic a typical canine maintenance food or the test food (n=21) which was controlled in protein, phosphorus and sodium and contained supplemental omega-3 fatty acids. There were significantly fewer episodes of uremic crises in the dogs fed the renal food compared with the control food (Figure 1) and significantly better quality of life as substantiated by a good Health Related Quality of Life index.⁶ Furthermore, the group of dogs fed the renal food lived greater than three times longer than the dogs fed the control food (Figure 2).²

Figure 1: Percentage of dogs that developed uremic crises while eating the renal food (nutrition of k/d[®]) compared with the control food (Control) during the study period



Figure 2: Median number of days until death in dogs eating the renal food (nutrition of k/d°) compared with the control food (Control) during the study period



NEW INNOVATIONS MAKE A PROVEN FOOD EVEN BETTER

MAINTENANCE OF LEAN BODY MASS

There is growing recognition among the veterinary profession that cachexia (the loss of LBM due to disease), and sarcopenia (the age-related loss of LBM) occur in our geriatric CKD patients. In humans, loss of LBM due to cachexia is directly associated with decreased survival time and quality of life.⁷ Veterinarians managing CKD patients have heightened interest in mitigating these debilitating effects nutritionally. Studies investigating the impact of controlled protein foods on geriatric cats and cats with CKD are available. Research in senior cats has confirmed that by formulating to an optimal lysine: calorie ratio as well as to an ideal protein content, dietary protein can be lowered without causing lean muscle mass loss. Healthy senior cats (n=12, average age 10 years) fed Prescription Diet[®] k/d[®] Feline for four months did not show significant changes in body weight and lean body mass as

measured by dual energy X-ray absorptiometry technology.⁸ In another study of cats with naturally occurring CKD (n=10) and healthy control cats (n=9), all cats maintained lean body mass and nitrogen balance when fed foods containing 20 and 24% metabolizable energy (ME) from protein.⁹ Both k/d[®] Feline canned and dry foods contain 22 and 23% ME from protein, respectively.

While studies have demonstrated that many pets with CKD fed a renal food maintain muscle mass, heightened awareness of this detrimental phenomenon has led to efforts aimed at further optimizing LBM in these at-risk patients. The mechanisms involved in cachexia are multifactorial and include changes in cytokine, catecholamine and insulin production, as well as changes in muscle fiber synthesis and type.⁷ In light of the significant role cachexia may play in the quality and quantity of life in pets with CKD, Hill's has recently updated k/d[®] Canine and Feline with a unique combination of omega-3 fatty acids from fish oil, high levels of carnitine and an enhanced essential amino acid profile (Figure 3), all incorporated to support a pet's natural ability to build lean muscle daily.

Figure 3: New and improved Prescription Diet[®] k/d[®] features and potential benefits

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Carnitine	Increases fat utilization as energy source, sparing muscle
Superior Amino Acid Profile	Supports the body's natural ability to build lean muscle daily
Enhanced Appetite Trigger (E.A.T.)™ Technology (for cats and for dogs)	Improved food/caloric intake, minimizing muscle catabolism

Among the added benefits of this update to k/d[®] Canine and Feline are **added L-carnitine** and omega-3 fatty acids from fish oil. Fatty acid oxidation is enhanced by carnitine, sparing oxidation of amino acids for energy metabolism that are instead used for protein synthesis (Owen, 2001).¹⁰ This may in part explain why healthy dogs and cats fed a complete and balanced diet with 300 and 500 ppm carnitine, respectively, gained significant LBM (P<0.01) compared with healthy control dogs and cats, as assessed by dual-energy X-ray absorptiometry.¹¹ Furthermore, mitochondrial efficiency has been shown to decrease with age and has been theorized to contribute to fatigue seen in aging humans. A study in healthy adult and geriatric dogs demonstrated that carnitine metabolites are reduced in geriatric dogs (>7 years) compared with mature dogs (\leq 7 years), but that this difference can be counterbalanced through carnitine supplementation (Hall).¹² Carnitine supplementation may help improve mitochondrial function in aging animals through improved efficiency of energy metabolism. This may in part explain why healthy, mature adult cats fed carnitine-enhanced food demonstrated improved overall youthful energy as reported by their owners (Ahle, 2009).¹³ Furthermore, carnitine is excreted primarily by the kidneys and is conserved by renal reabsorption (highly reabsorbed and conserved). In many species, reabsorption of carnitine is as high as 90%, but efficiency of reabsorption has been found to be impacted by kidney disease, further highlighting the rationale for supplementation in a renal supportive food (Carroll, 2001; NIH Carnitine Factsheet for Professionals).^{14,15}

Supplemental omega-3 fatty acids from fish oil have also shown promise in management

Figure 4: Limiting amino acid in current and new and improved k/d[®] Feline Chicken as a percentage of the AAFCO adult feline amino acid recommendations



of cachexia and sarcopenia. Omega-3 fatty acids from fish oil have been demonstrated to down regulate protein catabolism in cachexia through attenuation of proteasome expression, to decrease inflammatory cytokines, and to have benefits on muscle mass in dogs with cardiac cachexia.^{16,17} Studies investigating the beneficial effects of omega-3 fatty acids in management of sarcopenia suggest fish oil may further enhance protein synthesis in response to an anabolic substrate such as provision of amino acids.¹⁸ This is particularly noteworthy because k/d[®] Feline and Canine now contain the most optimal essential amino acid profile available for pets with CKD, including greater than 139 and 155% essential amino acids required by adult dogs and cats (US formula), respectively, as recommended by the Association of American Feed Control Officials (AAFCO). A study done at Hill's Pet Nutrition Center provided important evidence that increasing lysine and essential amino acids relative to lysine in a controlled protein food through the use of higher quality protein sources and added amino acids can maintain LBM similar to an increased protein food when fed to geriatric cats.¹⁹ In this study, they demonstrated that as the lysine:calorie ratio increased, loss of LBM was reduced.¹⁹ Furthermore, by providing greater than 139 and 155% of dogs' and cats' essential amino acid requirements, respectively, k/d[®] helps ensure that even pets with advanced CKD and decreased appetite are likely to meet their amino acid requirements necessary to prevent protein catabolism (Figure 4). The enhanced essential amino acid profile, added omega-3 fatty acids from fish oil, and increased levels of carnitine now present in k/d[®] Feline and Canine will provide further benefit to a food already proven to improve quality of life and decrease renal-related mortality in dogs and cats with CKD.



CHANGES IN FOOD INTAKE AND APPETITE

Pets with CKD may suffer from decreased appetite due to a variety of reasons, including uremia-related stomatitis, gastritis and nausea. Inadequate caloric intake further perpetuates loss of LBM in patients with CKD due to a lack of an adaptive response to inadequate caloric intake, which is seen in healthy pets. This lack of adaptive response to inadequate caloric intake results in failure of the body to utilize reserves in an orderly manner, and instead results in rapid degradation of tissue substrate stores. Therefore inadequate calorie intake is particularly important to address in patients with CKD. To further combat the causes of muscle loss in cats with CKD (in addition to the enhanced essential amino acid profile, added carnitine and omega-3 fatty acids from fish oil) Hill's recently introduced a new patent-pending flavor enhancing technology: Enhanced Appetite Trigger (E.A.T.)[™] Technology.

In a study of cats with CKD the average daily caloric intake of Prescription Diet® k/d® Feline dry with flavorenhancing E.A.T.™ Technology for cats was significantly greater than that of three of a key US competitor's feline renal dry food.²⁰ Cats fed k/d[®] Feline dry ate an average of up to 29.7% more calories daily compared with the competitor's renal dry food (**Figure 5**). This is an important component of the overall strategy to help maintain muscle in cats with CKD. Cats that eat adequate calories will also consume the right amounts of essential amino acids. In addition, L-carnitine functions to help the body efficiently utilize fat for energy thus helping to spare muscle.

In a study of 12 dogs with CKD, it was shown that the average daily caloric intake of Prescription Diet® k/d® Canine with Chicken dry with flavor-enhancing E.A.T.™ Technology for dogs was significantly greater than that of three of a key US competitor's canine renal dry foods.²¹ Dogs fed k/d® Canine with Chicken dry ate an average of up to 12.6% more calories than when compared to the competitor's renal dry food (**Figure 6**). An overall strategy of increasing caloric intake which helps ensure adequate essential amino acid intake in a food with added L-carnitine gives veterinarians another step towards successful long-term management of the canine CKD patient.

Figure 5: Average daily food intake of Prescription Diet® k/d® Feline dry with E.A.T.™ Technology for cats compared to competitor's foods



Figure 6: Average daily food intake of Prescription Diet® k/d® Canine with Chicken dry with E.A.T.™ Technology for dogs compared to competitor's foods

