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PROTEIN FOR CATS
With Chronic Kidney Disease

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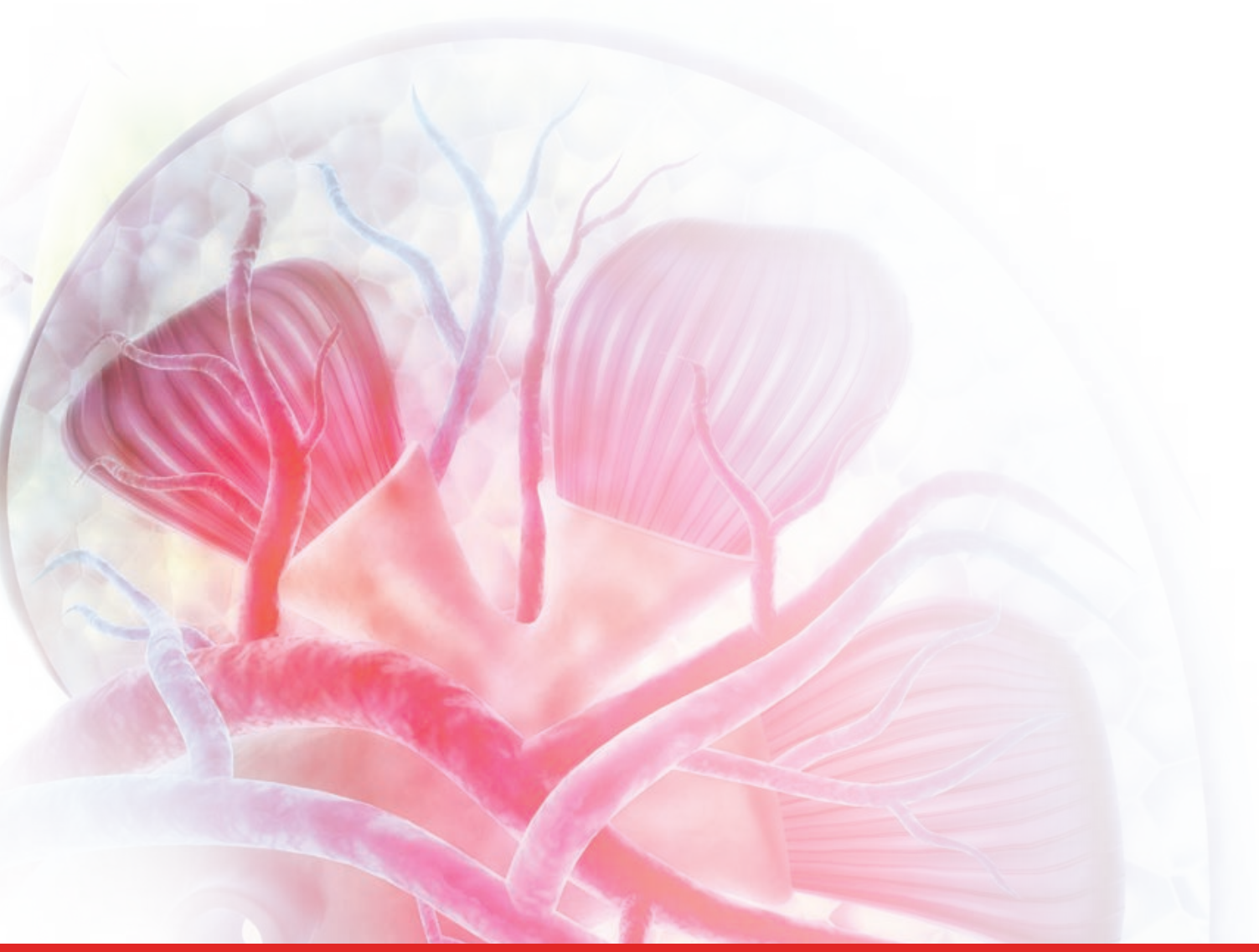
CHRONIC KIDNEY DISEASE IS A COMMON HEALTH CONCERN FOR SENIOR CATS

In recent decades, cats with chronic kidney disease (CKD) have been managed with diets restricted in protein and phosphorus. However, cats are a species with high protein requirements. A deficiency of protein contributes to loss of lean body mass and increases risk for mortality.[5] Medical advances that make earlier disease detection possible will enable clinicians to diagnose and stage cats with CKD more accurately and offer nutritional strategies that best meet the needs of each cat.



CONTENTS

KEY POINTS

- 1 out of 3 cats over the age of 10 years will be diagnosed with CKD[40]
- Nutritional management is a cornerstone of health care for cats with CKD
- Loss of lean body mass is associated with increased mortality in aging and in CKD[5,23]
- Maintaining higher protein levels in early stages of CKD may help preserve lean body mass
- Advances in early detection can improve CKD staging and nutrition strategies

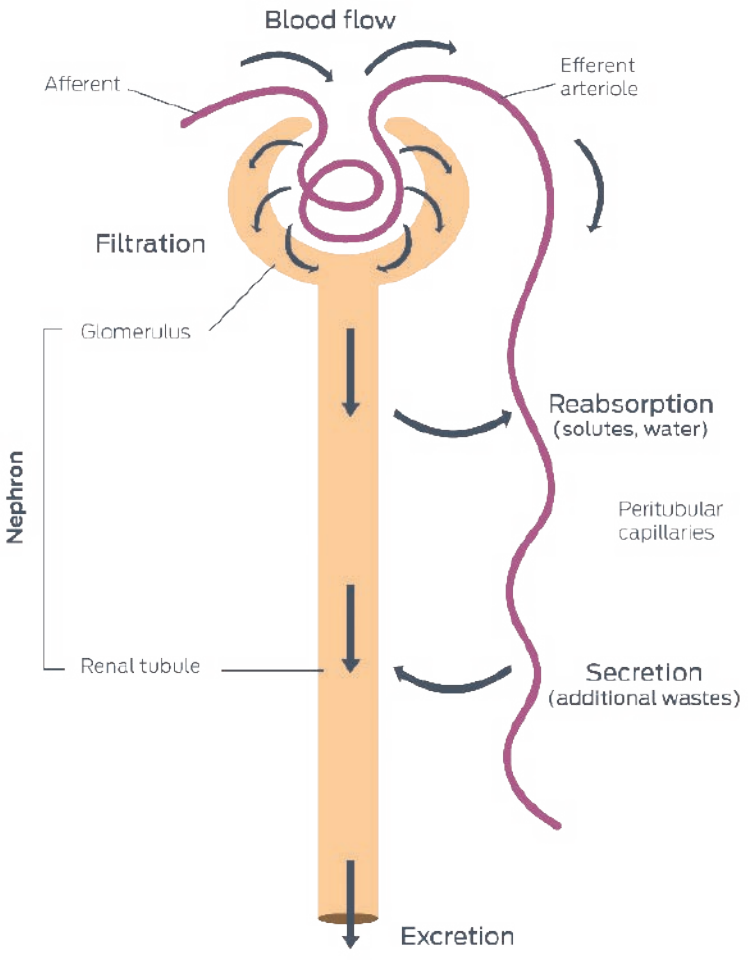
HEALTHY KIDNEY FUNCTION

Healthy kidneys filter metabolic waste and help maintain the balance of fluids and electrolytes. They also help regulate phosphorus levels and produce hormones that stimulate red blood cell production.

Nephrons are the functional unit of the kidney. Here, blood vessels from the body feed into the glomerulus, a high-pressure bundle of capillaries where the first step of filtration occurs.

The resulting filtrate then passes through a series of tubules where additional substances are added or absorbed back into the bloodstream before the fluid drains into collecting ducts that lead to the bladder.

There is no common cause for the development of feline kidney disease; more than 50% of cases are idiopathic, with no known cause. In cats with CKD, the kidneys are damaged by inflammation and progressive fibrosis of the tubules. This is in contrast to CKD in dogs, in which the glomerulus is more typically affected.[9]



CHRONIC KIDNEY DISEASE

Regardless of the inciting cause, CKD results in the progressive loss of nephrons. In early stages, undamaged nephrons compensate through hypertrophy and increased glomerular filtration rates (GFR). This response cannot be maintained indefinitely and, over time, the GFR declines. This slower rate leads to "leaky" filtration, resulting in rising serum levels of waste products—such as creatinine—that should have been removed, while protein that should be retained spills into the urine.

These dysfunctional conditions generate the key biomarkers currently used to monitor kidney disease progression: blood urea nitrogen (BUN), creatinine, phosphate, parathyroid hormone (PTH), calcium, sodium, and potassium in the serum, as well as urine specific gravity and protein in the urine.

More recently, symmetric dimethylarginine (SMDA) has been introduced as a biomarker for earlier detection of disease.[28] Fibroblast growth factor-23 (FGF-23) is another biomarker with prognostic potential.[24,25] The levels of these markers, along with signs of disease, help assess the cat's stage of CKD.

The International Renal Interest Society (IRIS) developed guidelines for staging CKD based on fasting plasma creatinine levels. These guidelines were adopted by the American and European Societies of Veterinary Nephrology and Urology.[30]

Feline CKD IRIS Stage	1	2	3	4
Plasma creatinine	< 1.6 mg/dl	1.6 - 2.8 mg/dl	2.9 - 5.0 mg/dl	> 5 mg/dl
SDMA	< 18 µg/dl	18 - 25 µg/dl	26 - 38 µg/dl	> 38 µg/dl

Source: http://www.iris-kidney.com/pdf/IRIS_Staging_of_CKD_modified_2019.pdf

NUTRITIONAL STRATEGIES

At any stage of renal disease, the goals of dietary management are: to provide complete nutrition; mitigate the clinical consequences of CKD, including signs of uremia; address changes in homeostasis that result from inadequate kidney function; slow disease progression and improve quality of life as well as life span.[30]

CKD is a slowly progressive disease. Cats may live with the disease for years, emphasizing the importance of providing adequate nutrition over the span of treatment for CKD.[17,25]

MAINTAIN LEAN BODY MASS

In healthy, aging cats maintaining body weight and lean body mass (LBM) is associated with reduced risk for mortality.[13]

Maintaining lean body mass requires adequate calorie and protein intake. Although studies show that cats can metabolically accommodate a range of protein levels once minimum protein needs are met, an inadequate intake of protein leads to loss of lean body mass.[27] Conversely, increased protein intake can reduce the loss of LBM.[36,37,45]

About 20% of senior cats have decreased protein digestibility, suggesting that older cats may have increased dietary protein needs. This age-related increase in protein needs was confirmed in studies of healthy aged cats.[12,46]

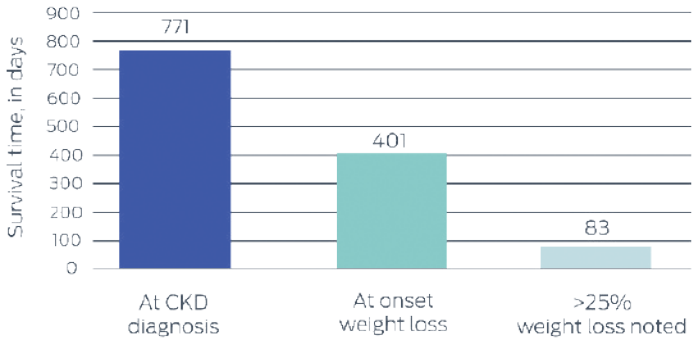
With age, cats naturally lose LBM. Cats with CKD may lose even more through metabolic changes or cachexia—the excessive loss of muscle in association with disease—which may alter strength, immune function and overall survival.[22]

Among 569 cats with CKD, those with a body weight at the time of diagnosis that was above the group median of **4.2 kg** had a significantly longer survival time than those at weights below this median.[23]

In both aging and CKD, losses in LBM or body weight are associated with increased mortality.[5,23,56]

The loss of body weight and LBM often begins before the kidney disease is recognized in cats.[23,28] Thus, preserving LBM and body weight are key nutritional factors for these felines.

Survival time and weight loss[5]



The evidence for higher protein needs in older cats, and increased risk for mortality with loss of body weight and LBM, suggests that protein restriction may not provide optimal nutrition for cats with early stage CKD.

DIETARY CHANGES MAKE A DIFFERENCE

Numerous studies have shown that therapeutic "renal diets" favor better clinical outcomes and can extend life span in cats with moderate to severe CKD when compared to feeding adult cat "maintenance" diets.[16,47,49]

The modifications to "renal diets" typically include: reduced protein and phosphorus, and added potassium, omega-3 fatty acids and antioxidants.[16,30,38,47-49] While studies clearly show that therapeutic diets have a positive impact on cats with CKD, the impact of protein is not defined at all. Among renal diets, protein is only one variable. In these studies, the diets not only varied in protein, but also phosphorus and other minerals, fatty acids, and buffering agents, all of which can affect kidney function.

Dietary Protein

The primary rationale for restricting dietary protein in cats with CKD is to reduce glomerular proteinuria and nitrogenous wastes, and slow progression of CKD. Yet clinicians also want to prevent weight loss, cachexia, and protein malnutrition in cats.

Several studies have shown that protein does not contribute to progression of renal disease.

In one study, cats with CKD that were fed a 51.7% protein diet developed more kidney problems than cats fed 27.6% protein.[1] But most of the cats fed the high-protein diet also developed hypokalemia because the diet was deficient in potassium; low potassium levels have a negative impact on kidneys and can induce kidney disease.[14] By the time the potassium deficiency was corrected in the study, these cats had numerous markers of advanced CKD, which then improved as the study progressed. Further, cats fed the low-protein diet consumed fewer calories, which may have a renoprotective effect.[34,52] Due to these confounding factors, any effects from protein levels could not be confirmed.

To tease out the effects of calories versus protein on CKD, Finco et al. studied four groups of cats with CKD that were fed either low protein-low calorie, low protein-high calorie, high protein-low calorie or high protein-high calorie diets.[19] After one year, only high caloric intake had a negative effect on kidneys. None of the cats fed high protein diets showed increased severity of renal lesions, increased proteinuria, or decreases in GFR relative to those fed the lower protein diets. These results were similar to study results in dogs, where protein levels had no negative effects on the kidneys, even in the face of CKD.[20]

A randomized, controlled study with geriatric cats in stage 1 CKD compared renal biomarkers of cats fed a 32% protein test diet with those on commercial maintenance diets.[29] After six months, cats on the 32% protein diet maintained urine concentrating ability and showed decreases in SDMA, creatinine and BUN while cats fed the owners' choice of foods had decreasing urine concentrations and elevated SDMA levels.

While the test diet was formulated with ingredients purported to have renoprotective effects, the protein level was much higher than typical renal diets and similar to many feline maintenance diets. This higher level of protein showed no adverse impact on renal biomarkers of early IRIS stage CKD cats.[20]

63% protein

The average percentage of dietary protein (on a dry matter basis) for a feral cat that "shops" for its own food.[35]

Phosphorus

The kidney is the primary route of phosphorus excretion. During the progression of CKD, if dietary phosphorus intake remains constant, the gradual decline in renal phosphorus clearance leads to increases in serum phosphorus concentrations (hyperphosphatemia).

Even before the onset of hyperphosphatemia, rising plasma phosphorus concentrations trigger a response in the parathyroid glands, which balance calcium and phosphorus levels. Additionally, elevated plasma phosphate also triggers increasing levels of FGF-23, a protein secreted by bone cells that acts to increase excretion of phosphate in the urine.

The parathyroid glands operate on a feedback system: high serum phosphorus stimulates increased PTH levels, leading to increased phosphorus and calcium resorption from bone. Secondary renal hyperparathyroidism, with elevated parathyroid hormone (PTH) concentrations has been reported in 84% of cats with CKD.[3]

Plasma phosphate is also a predictor for progression of feline CKD.[11] One study showed that an increase of 0.32 mmol/L (1 mg/dL) in plasma phosphate was independently associated with a 41% increase in the risk of progression (where progression is defined as a 25%, or greater, increase in plasma creatinine).[11]

Minimizing phosphorus retention and hyperphosphatemia appears to slow progression of CKD and prolong survival.[7,11] For these reasons, correction and prevention of hyperphosphatemia is a main concern in the management of CKD. Historically, this has been approached through restricting protein. Many protein ingredients have high phosphorus content, therefore reducing protein content helps reduce phosphorus intake.[42] However it is possible to formulate diets with lower phosphorus while maintaining normal protein levels.

A study in cats with CKD compared a normal phosphorus diet (1.56% phosphorus, dry matter) to a restricted phosphorus diet (0.42% phosphorus by dry matter). Results showed that lower levels of phosphorus reduced fibrosis, mineralization, and other adverse effects on kidneys. However, neither diet caused a significant change in measures of renal function over 343 days.[48]

Phosphate binders may aid in reducing serum phosphate accumulations in CKD, and may be used without restriction of dietary protein. In a model of CKD, researchers showed that cats fed maintenance diets and phosphate binders demonstrated decreases in serum phosphate and PTH levels.[8] Another study, in healthy cats, showed a phosphate binder was as effective as a low-phosphate diet at reducing urinary phosphate.[49]

Although CKD in dogs is different from the disease in cats, a two-year study of phosphorus and protein levels in dogs with CKD showed that survival was longer with low-phosphorus diets. The level of protein did not adversely affect survival, GFR, or renal morphology by the end of the study.[20]

Taken together, these studies show that restricting phosphorus—without restricting protein—can slow CKD progression.

In recent years, studies have also shown that higher plasma phosphate concentrations also trigger increasing levels of FGF-23, a protein secreted by bone cells that acts to increase excretion of phosphate in the urine.[26]

In people, plasma FGF-23 concentrations are an independent predictor of progression of CKD.[21] And in cats, studies show that increased FGF-23 at the time of CKD diagnosis is associated with an increased risk of progression of the disease over the next 12 months, as well as an increased risk of death.

A retrospective study linked lower plasma FGF-23 concentrations with feeding a phosphate-restricted diet in feline CKD patients, but it is not yet understood precisely why FGF-23 is associated with CKD progression in cats or whether targeted reduction of FGF-23 could improve survival time.[25]

More studies are needed to understand the complex interactions of FGF -23 in the kidney and parathyroid glands, but it may become a useful biomarker for predicting poorer outcomes.[39]

URINARY PROTEIN

When the renal glomeruli can't filter adequately, microscopic amounts of protein begin to appear in the urine, a condition called proteinuria. Increasing amounts of proteinuria are a poor prognostic indicator for CKD progression.[11,31,33,51]

In people with renal injury, high levels of dietary protein are correlated with increased proteinuria. This does not seem to be the case for cats. CKD in people most often begins with glomerular disease that is secondary to diabetes, hypertension, or other problems that have already compromised overall health and kidney function.[44]

However, when cats with CKD were fed varying levels of dietary protein, the levels of proteinuria were unrelated to protein intake.[19] Additionally, several studies that used angiotensin converting enzymes (ACE) inhibitors to manage proteinuria in cats with CKD showed that reductions in proteinuria were independent of protein intake.[6,50,55]

Overall, proteinuria is a poor prognostic indicator. In cats it appears unrelated to protein intake.

STAGING NUTRITION

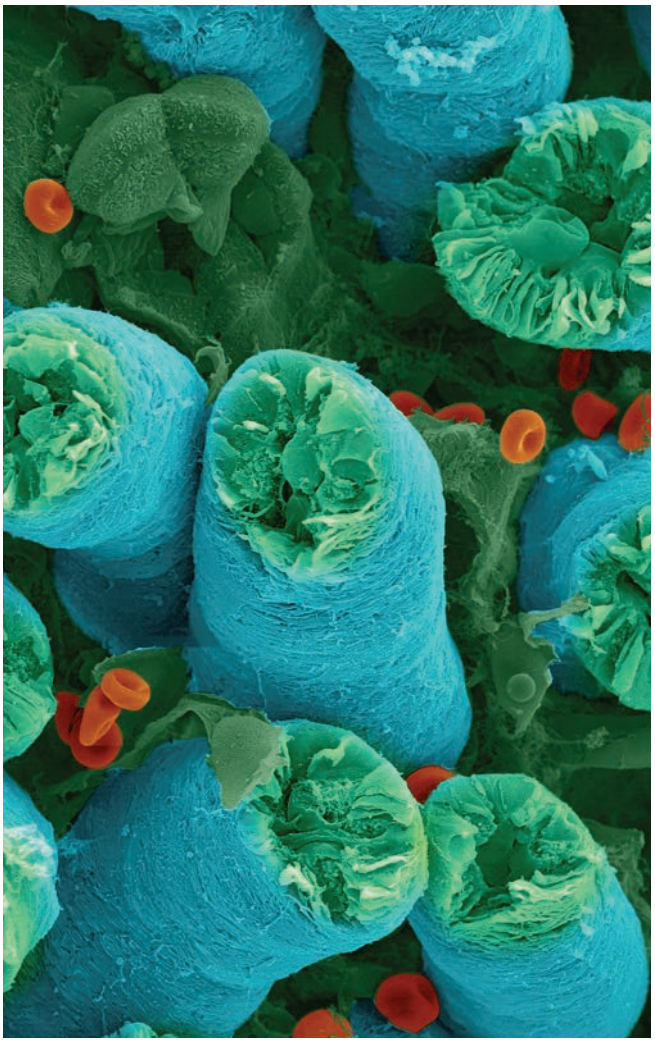
Nutritional management can help cats live with CKD for many years. The challenge is to balance the unique nutrient needs of cats with dietary modifications that will ameliorate clinical signs and slow progression of disease.

Studies show that higher dietary protein levels promote optimal body condition in aging cats and help reduce the natural, age-related loss of lean body mass.[57] And there are no clinical studies that have been conducted in cats with naturally occurring CKD in which dietary protein was the only variable evaluated. Based on the available evidence, protein restriction per se is not warranted in cats with CKD.[38]

With this in mind, in early stage CKD, higher levels of protein may help reduce loss of lean body mass, and the higher mortality rates associated with loss of lean body mass in aging cats.[36,37]

As CKD progresses, more moderate levels of protein may be needed while striving to maintain calorie intake and body weight.

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



Renal tubules

REFERENCES

1. Adams, L.G., Polzin, D.J., Osborne, C.A., & O'Brien, T.D. (1993). Effects of dietary protein and calorie restriction in clinically normal cats and cats with surgically induced chronic renal failure. *American Journal of Veterinary Research, 54*(10), 1653-1662.

2. Adams, L.G., Polzin, D.J., Osborne, C.A., O'Brien, T.D., & Hostetter, T.H. (1994). Influence of dietary protein/calorie intake on renal morphology and function in cats with 5/6 nephrectomy. *Laboratory Investigation, 70*(3), 347-357.

3. Barber, P.J., & Elliott, J. (1998). Feline chronic renal failure: calcium homeostasis in 80 cases diagnosed between 1992 and 1995. *Journal of Small Animal Practice, 39*, 108-116.

4. Barber, P.J., Rawlings, J.M., Markweu, P.J., & Elliott, J. (1999). Effect of dietary phosphate restriction on renal secondary hyperparathyroidism in the cat. *Journal of Small Animal Practice, 40*(2), 62-70.

5. Boyd, L.M., Langston, C., Thompson, K., Zivin, K., & Imanishi, M. (2008). Survival in cats with naturally occurring chronic kidney disease (2000-2002). *Journal of Veterinary Internal Medicine, 22*(5), 1111-1117.

6. Brown, S.A., Brown, C.A., Jacobs, G., Stiles, J., Hendi, R.S., & Wilson, S. (2001). Effects of the angiotensin converting enzyme inhibitor benazepril in cats with induced renal insufficiency. *American Journal of Veterinary Research, 62*(3), 375-383.

7. Brown, S., Crowell, W.A., Barsanti, J.A., White, J.V., & Finco, D.R. (1991). Beneficial effects of dietary mineral restriction in dogs with marked reduction of functional renal mass. *Journal of the American Society of Nephrology, 1*(10), 1169-1179.

8. Brown, S.A., Rickertsen, M., & Sheldon, S. (2008). Effects of an intestinal phosphorus binder on serum phosphorus and parathyroid hormone concentration in cats with reduced renal function. *International Journal of Applied Research in Veterinary Medicine, 6*(3), 155-160.

9. Brown, C.A., Elliott, J.A., Schmiedt, C.W., & Brown, S.A. (2016). Chronic kidney disease in aged cats: Clinical features, morphology, and proposed pathogeneses. *Veterinary Pathology, 53*(2), 309-326.

10. Burkholder, W.J., Lees, G.E., LeBlanc, A.K., Slater, M.R., Bauer, J.E., Kashtan, C.E., McCracken, B.A., & Hannah, S.S. (2004). Diet modulates proteinuria in heterozygous female dogs with X-linked hereditary nephropathy. *Journal of Veterinary Internal Medicine, 18*(2), 165-175.

11. Chakrabarti, S., Syme, H.M., & Elliott, J. (2012). Clinicopathological variables predicting progression of azotemia in cats with chronic kidney disease. *Journal of Veterinary Internal Medicine, 26*(2), 275-281.

12. Cupp, C.J., & Patil, A.R. (2010). *Addressing age-related changes in feline digestion. Proceedings of the Companion Animal Nutrition Summit: Focus on gerontology.* Clearwater Beach (FL), March 26-27, 62-69.

13. Cupp, C.J., Kerr, W.W., Jean-Philippe, C., Patil, A.R., & Perez-Camrgo, G. (2008). The role of nutritional interventions in the longevity and maintenance of long-term health in aging cats. *International Journal of Applied Research in Veterinary Medicine, 6*(2), 69-81.

14. DiBartola, S.P., Buffington, C.A., McLoughlin, M.A., & Sparks, R.A. (2003). Development of chronic renal disease in cats fed a commercial diet. *Journal of the American Veterinary Medical Association, 202*(5), 744-751.

15. Egenvall, A., Häggström, J., Ström Holst, B., Möller, L., & Bonnett, B.N. (2009). Mortality of life-insured Swedish cats during 1999-2006: Age, breed, sex, and diagnosis. *Journal of Veterinary Internal Medicine, 23*(6), 1175-1183.

16. Elliott, J., Rawlings, J.M., & Markwell, P.J., (2000). Survival of cats with naturally occurring chronic renal failure: effect of dietary management. *Journal of Small Animal Practice, 41*(6), 235-242.

17. Elliott, J., & Syme, H.M. (2006). Proteinuria in chronic kidney disease in cats: Prognostic marker or therapeutic target? *Journal of Veterinary Internal Medicine, 20*(5), 1052-1053.

18. Elliott, J., Syme, H.M., Reubens, E., & Markwell, P.J. (2003). Assessment of acid-base status of cats with naturally occurring chronic renal failure. *Journal of Small Animal Practice, 44*, 65-70.

19. Finco, D.R., Brown, S.A., Brown, C.A., Crowell, W.A., Sunvold, G., & Cooper, T.L . (1998). Protein and calorie effects on progression of induced chronic renal failure in cats. *American Journal of Veterinary Research, 59*(5), 575-582.

20. Finco, D.R., Brown, S.A., Crowell, W.A., Duncan, R.J., Barsanti, J.A., & Bennett, S.E. (1992). Effects of dietary phosphorous and protein in dogs with chronic renal failure. *American Journal of Veterinary Research, 53*(12), 2264-2271.

21. Fliser, D., Kollerits, B., Neyer, U., Ankerst, D.P., Lhotta, K., Lingenhel, A., Ritz, E., Kronenberg, F., MMKD Study Group, Kuen, E., König, P., Kraatz, G., Mann, J.F., Müller, G.A., Köhler, H., & Riegler, P. (2007). Fibroblast growth factor 23 (FGF23) predicts progression of chronic kidney disease: the Mild to Moderate Kidney Disease (MMKD) Study. *Journal of the American Society of Nephrology: JASN, 18*(9), 2600-2608. Doi: 10.1681/ASN.2006080936

22. Freeman, L.M. (2012). Cachexia and sarcopenia: Emerging syndromes of importance in dogs and cats. *Journal of Veterinary Internal Medicine, 26*(1), 3-17.

23. Freeman, L.M., Lachaud, M.P., Matthews, S., Rhodes, L., & Zollers, B. (2016). Evaluation of Weight Loss Over Time in Cats with Chronic Kidney Disease. *Journal of Veterinary Internal Medicine, 30*(5), 1661-1666.

24. Geddes, R.F., Finch, N.C., Syme, H.M., & Elliott, J. (2013). The role of phosphorus in the pathophysiology of chronic kidney disease. *Journal of Veterinary Emergency and Critical Care, 23*(2), 122-133.

25. Geddes, R.F., Elliott, J., & Syme, H.M. (2015). Relationship between plasma fibroblast growth factor-23 concentration and survival time in cats with chronic kidney disease. *Journal of Veterinary Internal Medicine, 29*(6), 1494-1501.

26. Geddes, R.F., Biourge, V., Chang, Y., Syme, H.M., & Elliott, J. (2016). The Effect of Moderate Dietary Protein and Phosphate Restriction on Calcium-Phosphate Homeostasis in Healthy Older Cats. *Journal of Veterinary Internal Medicine, 30*(5), 1690-1702. Doi: 10.1111/jvim.14563

27. Greene, A.S., Ramsey, J.J., Villaverde, C., Asami, D.K., Wei, A., & Fascetti, A.J. (2008). Cats are able to adapt protein oxidation to protein intake provided their requirement for dietary protein is met. *Journal of Nutrition, 138*(6), 1053-1060.

28. Hall, J.A., Yerramilli, M., Obare, E., Yerramilli, M., & Jewell, D.E. (2014). Comparison of Serum Concentrations of Symmetric Dimethylarginine and Creatinine as Kidney Function Biomarkers in Cats with Chronic Kidney Disease. *Journal of Veterinary Internal Medicine, 28*(6), 1676-1683. Doi: 10.1111/jvim.12445

29. Hall, J.A., MacLeay, J., Yerramilli, M., Obare, E., Yerramilli, M., Schiefelbein, H., Paetau-Robinson, I., & Jewell, D.E. (2016). Positive Impact of Nutritional Interventions on Serum Symmetric Dimethylarginine and Creatinine Concentrations in Client-Owned Geriatric Cats. *PloS one, 11*(4), e0153654. Doi: 10.1371/journal.pone.0153654

30. International Renal Interest Society. Staging of CKD. Available at: http://www.iris-kidney.com/pdf/IRIS_Staging_of_CKD_modified_2019.pdf

31. Jepson, R., Brodbelt, D., Vallance, C., Syme, H.M., & Elliott, J. (2009). Evaluation of predictors of the development of azotemia in cats. *Journal of Veterinary Internal Medicine, 23*(4), 806-813.

32. King, J.N., Tasker, S., Gunn-Moore, D.A., Gleadhill, A., & Strehlau, G. (2006). BENRiC (Benazepril in Renal insufficiency in Cats) Study Group. Tolerability and efficacy of benazepril in cats with chronic kidney disease. *Journal of Veterinary Internal Medicine, 20*(5), 1054-1064.

33. King, J.N., Tasker, S., Gunn-Moore, D.A., & Strehlau, G. (2007). BENRIC (benazepril in renal insufficiency in cats) Study Group. Prognostic factors in cats with chronic kidney disease. *Journal of Veterinary Internal Medicine, 21*(5), 906-916.

34. Kobayashi, S., & Venkatachalam, M.A. (2002). Differential effects of calorie restriction on glomeruli and tubules of the remnant kidney. *Kidney International, 42*(3), 710-717.

35. Kremen, N.A., Calvert, C.C., Larsen, J.A., Baldwin, R.A., Hahn, T.P., & Fascetti, A.J. (2013). Body composition and amino acid concentrations of select birds and mammals consumed by cats in northern and central California. *Journal of Animal Science, 91*(3), 1270-1276.

36. Laflamme, D.P., & Hannah, S.S. (2005). Increased dietary protein promotes fat loss and reduces loss of lean body mass during weight loss in cats. *International Journal of Applied Research in Veterinary Medicine, 3*(2), 62-68.

37. Laflamme, D.P., & Hannah, S.S. (2013). Discrepancy between use of lean body mass or nitrogen balance to determine protein requirements for adult cats. *Journal of Feline Medicine and Surgery, 15*(8), 691-697.

38. Laflamme, D., Backus, R., Brown, S., Butterwick, R., Czarnecki-Maulden, G., Elliott, J., Fascetti, A., & Polzin, D. (2020). A review of phosphorus homeostasis and the impact of different types and amounts of dietary phosphate on metabolism and renal health in cats. *Journal of Veterinary Internal Medicine, 34*(6), 2187-2196. Doi: 10.1111/jvim.15961

39. Lin, J., Lin, L., Chen, S., Yu, L., Chen, S., & Xia, Z. (2021). Serum fibroblast growth factor 23 (FGF-23): associations with hyperphosphatemia and clinical staging of feline chronic kidney disease. *Journal of veterinary diagnostic investigation: official publication of the American Association of Veterinary Laboratory Diagnosticians, Inc, 33*(2), 288-293. Doi: 10.1177/1040638720985563

40. Lulich, J.P., Osborne, C.A., O'Brien, T.D., & Polzin, D.J. (1992). Feline renal failure: Questions, answers, questions. *Compendium of Continuing Education for Practicing Veterinarians, 14*(2), 127-151.

41. Lumlertgul, D., Burke, T.J., Gillum, D.M., Alfrey, A.C., Harris, D.C., Hammond, W.S., & Schrier, R.W. (1986). Phosphate depletion arrests progression of chronic renal failure independent of protein intake. *Kidney International, 29*(3), 658-666.

42. MacKay, E.A., & Oliver, J. (1935). Renal damage following the ingestion of a diet containing an excess of inorganic phosphate. *Journal of Experimental Medicine, 61*, 319-336.

43. Morris, J.G. (2002). Idiosyncratic nutrient requirements of cats appear to be diet-induced evolutionary adaptations. *Nutritional Research Review, 15*(1), 153-168.

44. Noguiera, A., Pires, M., & Oliveira, P. (2017). Pathophysiological mechanisms of renal fibrosis: A review of animal models and therapeutic strategies. *in vivo, 31*(1), 1-22.

45. Nguyen, P., Leray, V., Dumon, H., Martin, L., Siliart, B., Diez, M., & Biourge, V. (2004). High protein intake affects lean body mass but not energy expenditure in nonobese neutered cats. *Journal of Nutrition, 134*(8 Suppl), 2084S-2086S.

46. Perez-Camargo, G. (2004). Cat nutrition: what's new in the old? *Compendium of Continuing Education for Practicing Veterinarians, 26*(S2A), 5-10.

47. Plantinga, E.A., Everts, H., Kastelein, A.M.C., & Beynen, A.C. (2005). Retrospective study of the survival of cats with acquired chronic renal insufficiency offered different commercial diets. *Veterinary Record, 157*(7), 185-187.

48. Ross, L.A., Finco, D.R., & Crowell, W.A. (1982). Effect of dietary phosphorus restriction on the kidneys of cats with reduced renal mass. *American Journal of Veterinary Research, 43*(6), 1023-1026.

49. Ross, S.J., Osborne, C.A., Kirk, C.A., Lowry, S.R., Koehler, L.A., & Polzin, D.J. (2006). Clinical evaluation of dietary modification for treatment of spontaneous chronic kidney disease in cats. *Journal of the American Veterinary Medical Association, 229*(6), 949-957.

50. Sent, U., Gössl, R., Elliott, J., Syme, H.M., & Zimmering, T. (2015). Comparison of Efficacy of Long-term Oral Treatment with Telmisartan and Benazepril in Cats with Chronic Kidney Disease. *Journal of Veterinary Internal Medicine, 29*(6), 1479-1487.

51. Syme, H.M., Markwell, P.J., Pfeiffer, D., & Elliot, J. (2006). Survival of cats with naturally occurring chronic renal failure is related to severity of proteinuria. *Journal of Veterinary Internal Medicine, 20*(3), 528-535.

52. Tapp, D.C., Kobayashi, S., Fernandes, G., & Venkatachalam, M.A. (1989). Protein restriction or calorie restriction? A critical assessment of the influence of selective calorie restriction in the progression of experimental renal disease. *Seminars in Nephrology, 9*(4), 343-353.

53. Theisen, S.K., DiBartola, S.P., Radin, M.J., Chew, D.J., Buffington, C.A., & Dow, S.W. (1997). Muscle potassium content and potassium gluconate supplementation in normokalemic cats with naturally occurring chronic renal failure. *Journal of Veterinary Internal Medicine, 11*(4), 212-217.

54. Toblli, J.E., Bevione, P., Di Gennaro, F., Madalena, L., Cao, G., & Angerosa, M. (2012). Understanding the Mechanisms of Proteinuria: Therapeutic Implications. *International Journal of Nephrology, 2012*, 546039.

55. Watanabe, T., & Mishina, M. (2007). Effects of benazepril hydrochloride in cats with experimentally induced or spontaneously occurring chronic renal failure. *Journal of Veterinary Medical Science, 69*(10), 1015-1023.

56. Wolfe, R. (2006). The underappreciated role of muscle in health and disease. *American Journal of Clinical Nutrition, 84*(3), 475-482.

57. Zoran, D., & Buffington, C.A. (2011). Effects of nutrition choices and lifestyle changes on the well-being of cats, a carnivore that has moved indoors. *Journal of the American Veterinary Medical Association, 239*(5), 596-606.

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