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Nutrition – a corner stone for management of urinary tract disorders Mini Series

Session One: Too much pee! Updates in nutritional management of chronic kidney disease

Marge Chandler DVM, MS, MANZCVSc, DACVN, DACVIM,MRCVS

Dietary therapy is a crucial part of management of chronic kidney disease (CKD) in dogs and cats. Therapeutic diets formulated for renal disease improve survival time, reduce uraemic crisis episodes, improve serum urea nitrogen and phosphorus concentrations and decrease fibroblast growth factor 23 (FGF-23), a hormone associated with poorer survival time. When food intake is adequate it may be possible for pets to maintain body weight and condition score for up to two years. Nutritional management with a diet formulated for renal disease is recommended in dogs and cats with International Renal Interest Society (IRIS) Stage 2 and higher to slow progressive loss of kidney function, reduce clinical and biochemical consequences of CKD, and maintain adequate nutrition. The use of diets for renal disease in IRIS Stage 1 is more controversial.

Assessment of diet and patient

A complete nutritional assessment as per the WSAVA guidelines (https://wsava.org/nutrition-toolkit) should be performed at every visit. The diet history should include any extra foods fed as owners will often be using treats and human foods to encourage food intake or to give medications.

A body condition score should be performed, ideally with the 9 point method. Poor body condition is associated with a poorer prognosis in cats and dogs with CKD, so adequate food intake is vitally important. Muscle mass should also be evaluated at each visit. It can affect serum creatinine and should be considered when serum creatinine appears to be" improving" in a pet which is not clinically better, i.e. the decreased creatinine may be due to decreased muscle mass.

Hydration

Unrestricted access to water is essential for CKD patients to compensate for solute dieresis and urinary water loss. Older pets may not sense thirst well compared to younger pets and may need encouragement to take in enough fluids to prevent dehydration. Provide easy access to water, for example, some cats like running water. For pets with mobility problems like arthritis, water bowls should be located in easy to access areas or even elevated. They should be placed in more than one area of the house and away from food bowls and litter boxes. Adding water to the food may be beneficial. For cats, feeding a canned food will result in more fluid intake than feeding dry food plus water.

Some cats benefit from intermittent IV or SQ crystalloid fluids and owners may be taught to provide SQ fluids (Korman and White 2013). Owners need to understand that restricting water will not decrease the polyuria of CKD and may result in the death of the pet.

Calories

Poor body condition is associated with a shorter survival time and poor appetite is perceived as a significant quality of life concern by owners. Renal diets are high in energy density, i.e. low in fibre and high in fat. Fat is a palatable and high calorie source of energy. This helps facilitate calorie intake even in the face of a waxing and waning appetite. Dry foods are more energy (calorie) dense than canned foods.

While pets on commercial diets for renal disease have significantly better survival than those on maintenance diets, there are some pets which will refuse to eat the diet. In one study only about half of the cats with CKD were on a veterinary therapeutic diet for renal disease (Markovich et al 2015).

Early use of the diets, for example using early renal diets during IRIS Stage 1, and a slow transition will help prevent this. In one study the transition period ran for 6 weeks or longer (Ross et al., 2006). In this study, 94% of the cats were successfully transitioned on to the therapeutic diet. Having the cat eat 80% of its intake from the renal diet was considered acceptable for the study. Adding low protein low phosphorus flavouring agents like tuna water or low salt chicken broth was used to increase the palatability when the cats' intake was insufficient. During the transition period, the new food should be mixed with the old food

in increasing amounts. If these methods fail, using a home-made diet formulated for kidney disease may be tried. Note that nearly all homemade diets in books and on the web are not complete and balanced for pets with kidney disease (Larsen et al 2012). Tube feeding is also an option for short or long term alimentation. Oesophagostomy (or gastrotomy)tubes are useful for long term feeding and usually well accepted by the pets.

Diets formulated for senior cats may be (or may not be) lower in phosphorus than adult maintenance diets, and are another consideration. Phosphate binders should be added as needed to control serum phosphate, although this is not ideal as control of phosphorus is seldom as good using a phosphate binder with an adult or senior diet as when feeding a therapeutic diet. Further, diets for renal disease also have other positive attributes such as improving acid-base balance, increased B vitamins, omega-3 fatty acids, and anti-oxidants.

Appetite, Anti-emetics and Appetite stimulants

Nausea, vomiting and poor appetite are common in patients with CKD. Uraemic toxins are sensed by the chemoreceptor trigger zone in the brain, stimulating nausea and vomiting. In one study 43% of 1079 cat owners reported that their cats had an abnormal appetite. Of these owners, 52% responded that their cats had a poor appetite or required coaxing to eat 5 to 7 days per week (Markovich et al., 2015).

In another study, while 90.8% of all owners of cats with CKD had received a recommendation to feed a therapeutic renal diet, only 66.47% reported that they were feeding a one as a component of their cat's diet. The most common reason for not feeding the renal diet was that the cat did not like it (n = 123; 59.13%). Where a veterinary recommendation to feed a renal diet had been received, 564 owners (72.31%) reported feeding it as a component of their cat's diet, demonstrating the importance of making the recommendation and helping the owner with the transition (Caney, 2017).

Several potentially helpful anti-emetics and appetite stimulants are available including the NK_1 receptor antagonist maropitant. Metoclopramide has a short half-life and has largely been replaced with other anti-emetics for patients with CKD. Maropitant is often used for acute vomiting, although longer term use appears to be safe (Quimby 2016).

Although more often used as an appetite stimulant, mirtazapine also decreases vomiting in cats with CKD. Its use was originally limited by side effects of vocalization, hyperexcitability and tremors, although when given at a lower dose of 1.88 to 2.0 mg per cat every other day it has positive effects on appetite and fewer side effects. In cats with chronic kidney disease the mean half-life is 15.2 hours. Dogs may need to be dosed twice a day as the half life is shorter. A transdermal product has been tested in the USA in cats and shown good efficacy. While this non-compounded product is not yet available in the UK there is a compounded one available.

Cyproheptadine (2-4 mg/cat q 12-24 hr) has been used as an appetite stimulant in cats as well; note that it cannot be given concurrently with mirtazapine as it is the antidote for mirtazapine over dose and will negate the effect.

Capromorelin, a ghrelin agonist, may also be useful as an appetite stimulant in the future, at least for short term use (e.g. in hospital). It is licensed for dogs in the USA, but not yet available in the UK. Currently, in pets who tolerate it well, mirtazapine appears to be the appetite stimulant of choice for pets with CKD.

The use of H2 blockers or proton pump inhibitors anecdotally appears to improve appetite in some patients: however, both the degree of hyperacidity present in CKD and the efficacy of these medications in CKD remains unproven. Omeprazole has been demonstrated to be superior to famotidine in inhibiting acid production with 1 mg/kg twice daily dosing, although probably should not be used long term.

Protein

While dietary protein restriction has long been advocated for the management of CKD, the optimal amount of protein for patients with kidney disease is not really known as protein restricted diets are also usually phosphorus restricted and the effects of the two parameters are difficult to separate.

Lower protein diets have been thought to slow the rate of progression of renal disease, although this concept is controversial and the effects of the diets may be due to the lower phosphorus. Higher protein diets do not appear to increase the risk of developing kidney disease. Renal diets usually provide less protein than maintenance diets to reduce the amount of nitrogenous waste products. On the other hand, in humans, there is some evidence that a lower protein diet may slow progression and reduce deaths from renal disease in CKD patients.

Protein should be provided in adequate amounts and be of a high biological value, to avoid creating essential amino acid deficiencies. The NRC minimum protein requirement is around 16% protein calories, while AAFCO's is 22%. Most renal diets range from 22 to 27%, and all of them provide all amino acid requirements. However, in patients with poor appetite that do not eat enough, the energy deficiency will result in muscle mobilization and in a decreased protein intake, making them prone to protein malnutrition. Thus, there is concern that the lower protein of diets for renal disease contributes to sarcopenia, and certainly a very low protein diet will result in a decrease of muscle mass as muscles are catabolized for protein. Factors other than dietary protein contribute to energy protein malnutrition in CKD, including increased energy expenditure, decreased physical activity (e.g. disuse atrophy of muscles) persistent inflammation, and metabolic acidosis.

There have been some recent unfounded recommendations to feed higher amounts of protein or maintenance diets to cats with CKD; this is potentially harmful to cats with IRIS Stages 3 and 4. These diets are also too high in phosphorus and lack many of the other nutritional attributes of diets for renal disease and this practice is NOT recommended.

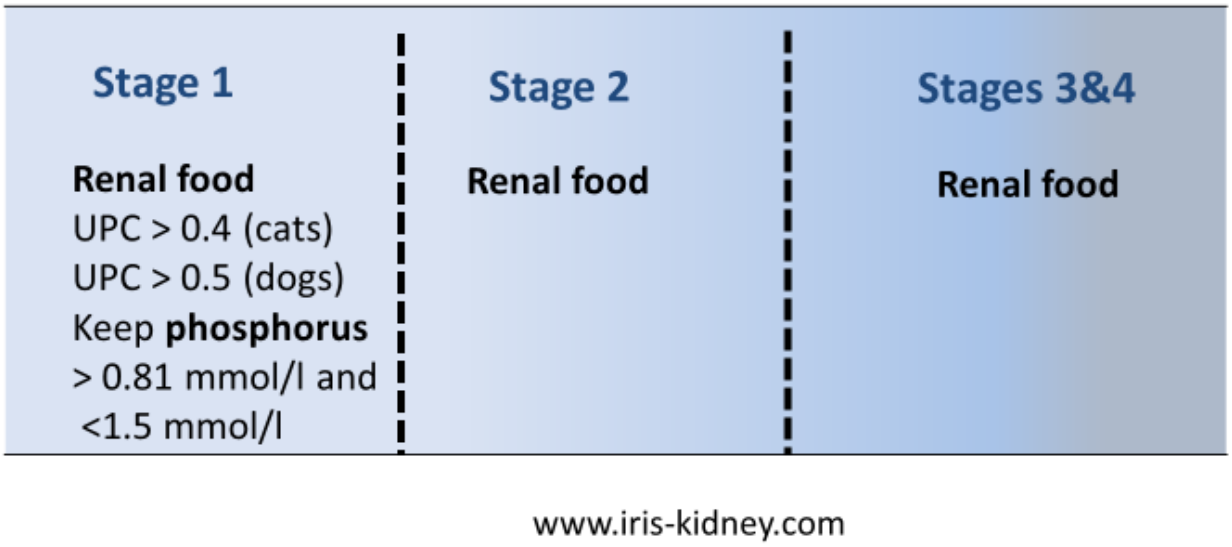
However, a retrospective study investigated the impact of a one month amino acid supplementation on body weight, serum albumin, creatinine and urea concentrations, and urine protein-to-creatinine (UPC) ratio in 46 proteinuric dogs with chronic kidney disease. Both treated and control dogs were fed diets for renal disease. While the control dogs had a decreased urea compare to supplemented dogs, the supplemented dogs had increased body weight and serum albumin concentration dogs compared to the controls. The authors proposed the use of amino acid supplementation in proteinuric dogs with severe hypoalbuminemia that are not adequately controlled with standard treatments consisting of renal diets and ACE inhibitors (Zatelli, et al., 2017).

International Renal Interest Society (IRIS) Stages 2-4

Controlled restriction of non-essential protein will reduce the accumulation of the nitrogenous waste products which contribute to the uraemic syndrome, and may also decrease acidosis. In one study cats in IRIS stage 2 or 3 fed a diet for renal disease showed decreased serum urea nitrogen and increased blood bicarbonate, but there was no difference in serum creatinine, potassium, calcium, or parathyroid hormone concentration or urine protein to creatinine ratio. The cats on the diet for renal disease showed fewer uraemic episodes and less renal disease associated deaths (Ross et al 2006).

Recommendations for protein restriction in cases where overt signs of CKD (IRIS Stages 2to 4) are present vary and have included 28 to 35% dry matter basis for dogs and cats, (Forrester, et al., 2010), and for cats 20 to 40% of calories (Scherk and Laflamme, 2016).

Table 1. IRIS Recommendations for Renal Diet in patients with Proteinuria:



IRIS Stage 1

Now that we have better methods of diagnosis renal disease earlier with the use of symmetric di-methyl arginine decisions about treatment in IRIS Stage 1 are more common. The use of diets for renal disease in IRIS Stage 1 has been controversial due to the lower protein content of many of these diets. Introducing a diet change early doesimprove diet acceptance. Over 90% of cats with CKD accepted renal diets when a very gradual transition was used (Ross et al 2006).

IRIS Stage 1 in cases with significant proteinuria, i.e. urine protein to creatinine ratio (UPC) of >0.4 for cats and >0.5 for dogs, or serum phosphorus above the reference range has been an indication for a feeding a diet for renal disease. The lower protein of these diets can help

For pets without proteinuria or hyperphosphataemia, the indication of a feeding diet for renal disease has previously been less clear. In a 12-month feeding trial in dogs with IRIS-Stage 1 CKD,renal biomarkers, including serum creatinine (Cr), blood urea nitrogen (BUN), and symmetric dimethylarginine (SDMA),were significantly decreased from baseline at 3-months, and remained decreased from baseline at 12-months, in dogs completing the study. Proteinuria was reduced in 12 of the 16 dogs with proteinuria (Hall et al., 2018). The decreasing serum biomarker concentrations and reduction in proteinuria suggest stabilized kidney function.

Similarly, a study in feeding a diet for renal disease to cats with CKD which included IRIS Stage 1 cats found that the renal parameters (serum creatinine and BUN) of IRIS Stage 1 cats were unchanged in between baseline and after 12 months (Hall, et al., 2019). Neither of these studies were controlled, which makes the conclusions more difficult to assess, but renal disease is usually progressive so the lack of progression is promising.

Again, the potential drawback of feeding a diet for renal disease is the lower protein, as protein is necessary for all body functions and decreasing muscle mass is a poor prognostic indicator for survival times. Cats have a higher requirement for protein than dogs, and the concerns are more for cats. Diets formulated for renal disease are above the AAFCO and FEDIAF lower limits for protein on a dry matter basis. They are also just above the FEDIAF protein requirement of 62.5 g protein/1000 kcal on a metabolizable energy content for cats with a higher energy requirement (100 kcal ME/kg$^{0.67}$. For cats with

lower energy intake (75 kcal ME/kg$^{0.67}$) they may fall below the 83.3 g protein/ 1000kcal FEDIAF protein minimum.

The quality of protein is also important, as lower amounts may be sufficient if the essential amino acid requirement (i.e. biological value) is met plus enough of the non-essential amino acids are provided. The digestibility of the protein is also important.

There are no diets formulated for the earlier stages of renal disease which contain higher amounts of protein than those recommended for later stages. For IRIS Stage 1, in some cases a senior diet which meets the nutrient for early renal disease could also be considered.

Renal Secondary Hyperparathyroidism and Phosphorus (RHPTH)/ Metabolic Bone Disease (MBD)

Pathogensis

Renal hyperparathyroidism (RHPTH) is implicated as a cause of intrinsic progression as well as contributing to the uraemia of CKD.

The main cause of RHPTH is the continued intake of phosphorus exceeding the ability of the diseased kidneys to excrete it. Phosphorus retention initially increases fibroblast growth factor 23 (FGF-23) from fibroblasts and later increases synthesis of PTH. FGF-23 decreases phosphorus reabsorption in the proximal renal tubule, decreases intestinal phosphate absorption via decreased conversion of calcidiol to calcitriol, and increases synthesis of PTH. PTH also decreases renal phosphorus absorption but increases the synthesis of calcitriol from calcidiol. Initially these effects keep serum phosphorus in the reference range at the expense of increases serum PTH and FGF-23. Some IRIS Stage 1 dogs have evidence of RHPTH which precedes hyperphosphataemia, and cats may have elevated serum FG-23 prior to azotaemia and PTH prior to hyperphosphataemia. All IRIS Stage 4 patients have RHPTH.

PTH stimulates osteoclast activity to release calcium into the blood to help correct hypocalcaemia. This excess parathyroid hormone (PTH) and osteoclast activity causes the demineralization of bone, leading to the various changes termed renal osteodystrophy (e.g. rubber jaw). Evidence suggests that bone quality is decreased in companion animals with CKD, more pronouncedly in cats compared with dogs, likely because of a longer disease course.

Increased serum phosphorus and calcium concentrations can lead to soft tissue mineralization, including potential vascular mineralization.

Treatment

The goals of treatment are to restrict phosphate intake, prevent or decrease bone loss, and prevent or decrease soft tissue mineralization. For each 1 mg/dl increase in the blood level of phosphorus, there is an 11.8% increase in the risk of death (Boyd et al., 2008). The first of the treatment goals is dietary phosphate restriction. Recommended phosphorus concentrations in the diet are usually 0.3 to 0.6% dry matter basis for cats or generally below 1g/1000 kcal. Dietary modification using commercially available renal diets which restrict phosphorus significantly increases survival in CKD (Elliot J et al 2000; Ross et al 2006).

As well as the effects on phosphorus and PTH, feeding phosphorus restricted renal diet is associated with reductions in plasma FGF-23 concentrations in hyper- and normophosphatemic cats with stable azotaemic CKD, suggesting that dietary phosphate restriction may enable cats with CKD to maintain normal plasma phosphate concentrations in association with lower plasma FGF-23 concentrations (Geddes et al.,2013)

There is currently no safe upper limit for phosphorus listed by FEDIAF for healthy adult cats, although research is ongoing. Recent research indicates that, at least in cats, the form of the phosphorus, e.g. what it is complexed with such as sodium dihydrogen phosphate, may also have an effect on the kidneys. The calcium to phosphorus ratio is also important . The intake of a diet with an excessive content of

highly available phosphorus may have adverse effects on parameters of kidney function even in healthy cats (Dobenecker et al, 2018).

If plasma phosphate concentration remains elevated (see Table 2) after dietary restriction enteric phosphate binders (e.g. aluminium hydroxide, aluminium carbonate, calcium carbonate, calcium acetate, lanthanum carbonate) should be given to effect (i.e. to lower the serum phosphorus to below 1.5 mmol/l or the appropriate target level per IRIS Stage).

Table 2. Serum phosphorus targets (adapted from Foster, 2016)

IRIS CKD Stage	Target Serum Phosphorus (mmol/l)
1	Reference range
2	0.81 – 1.5
3	0.81 – 1.60
4	0.81 – 1.95

Starting doses of phosphate binders are 30-60 mg/kg/day in divided doses, mixed with the food. It is pointless to give phosphate binders to animals which are not eating as the phosphate binders combine with food to decrease absorption in the intestine. Signs of toxicity limit the upper dose rate possible. Monitor serum calcium and phosphate concentrations every 4 to 6 weeks until stable and then every 12 weeks. Microcytosis and/or generalized muscle weakness suggests aluminium toxicity if using an aluminium containing binder. If these occur switch to another form of phosphate binder. Hypercalcaemia and hypocalcaemia should be avoided. Cats with serum phosphate within the IRIS target may be at increased risk ofdeveloping hypercalcemia when renal diets are introduced. If total serum calcium exceeds 3 mmol/l consider switch the cat to a senior diet or mix renal diet (50:50 by volume) with a maintenance diet; however, other aspects and attributes of renal diets should be considered.

Treatment with an active form of vitamin D, (calcitriol or alphacalcidol) has been recommended to directly inhibit PTH secretion. This should be used only after the serum phosphorus has been controlled. This group of drugs has a narrow therapeutic index due to their tendency to cause hypercalcaemia and careful monitoring is needed when they are used (Polzin D e.t al, 2008).

In one random controlled masked study a of 31 dogs fed a renal diet with or without a commercial dietary supplement containing chitosan, phosphate binders, and alkalinizing agents fed a renal diet for 44 weeks, the supplemented dogs had approximately 50% lower mortality rate due to uremic crises ($p = 0.015$) (Zatelli et al., 2012).

<u>Metabolic Complications</u>

Hypokalaemia and Hyperkalaemia

Potassium varies amongst renal diets (from 1.5 to 3.5 g/1000 Kcal, approximately). The best choice will depend on the patients since some renal patients will be hypokalemic (common in cats) but some will be hyperkalemic, for example late stage patients and those receiving ACE inhibitors. When hyperkalaemia occurs, appropriately formulated, potassium-reduced, diets can be an effective alternative to correct it (Segev, et al., 2010)

Hypokalaemia occurs in 20 to 30% of cats with CKD and by the time serum concentrations are low the body is depleted, so the problem may be more extensive subclinically. Metabolic acidosis causes potassium to move extracellularly an acidifying diet lower serum potassium concentration. This may be via an increase in aldosterone and/or a decrease in renin.

Oral potassium supplementation should be used in any cat with persistent hypokalaemia as this has been associated with muscle weakness (especially ventroflexion of the neck) and morphological renal abnormalities and can worsen CKD. Recommended oral potassium supplementation doses are 3 to 5

mEq/kg body weight per day and various forms are available. Most diets for feline renal disease contain increased potassium.

Acid-base balance

Metabolic acidosis is common with CKD as the kidneys play a major role in acid base balance and may be less able to reabsorb bicarbonate. Acidosis can cause a decreased appetite, vomiting, lethargy, weakness and increased protein catabolism which can contribute to decreased lean body mass and sarcopenia. IRIS guideline suggestions are that the blood bicarbonate (TCO_2) be maintained between 16 and 25 mmol/l in a stable and hydrated patient. Most diets for renal disease are non-acidifying and alkalinizing. If needed, potassium citrate or sodium bicarbonate can be supplemented (although note comments on sodium below).

Sodium Restriction

Increased dietary sodium has been associated with increased azotaemia in one study in cats (Kirk et al 2006), and is thought to contribute to signs of uraemia in people. This concept is still controversial, and 2-year study in older healthy cats did not find any association between salt consumption and glomerular filtration rate(Reynolds et al 2013).

Recommended sodium levels in cases of feline CKD are thought to be between 0.2 to 0.35 DMB. Sodium does not appear to affect blood pressure in dogs or cats unless it is at excessively high levels and there is not any obvious association with sodium and hypertension in cats. And Restriction of sodium can activate the renin-angiotensin-aldosterone (RAAS) system can cause progression of the renal disease and can also increase potassium losses.

B Vitamins

As the B vitamins are water soluble, increased urine output results in an increased loss of these nutrients. A diet supplemented with B vitamins is recommended, especially in cats, which have an increased requirement for B vitamins compared to dogs. Most commercial diets for renal disease have increased amounts of B vitamins added.

Fats and Omega 3 Fatty Acids

Commercial renal are often high in fat, which increases the caloric density and can be useful for help maintain body weight; however, pets with pancreatitis, hyperlipidaemia, or lymphangiectasia require a low-fat diet. These pets often require a specially formulated homemade diet to balance their requirements

Omega 3 fatty acids (e.g. fish oils) modify the inflammatory response and have been shown to be useful in kidney disease, especially glomerulonephritis (Bauer 2007). A role for omega-3 polyunsaturated fatty acid supplementation in the reduction of glomerular hypertension, proteinuria and in limiting production of inflammatory mediators such as prostaglandin E2 and thromboxane A1 has been postulated for dogs.

Omega 3 fatty acids may reduce proteinuria. Palatability of omega 3 supplements seems to vary among pets, with some liking fish oils and others refusing to eat fish oil supplemented foods. Many of the diets for renal disease include increased omega 3 fatty acids.

Antioxidants

Renal oxidant stress has been suggested to play a role in the progression of CKD. Chronic hypoxia and renal ischaemia, as a result of either reduction in renal perfusion or anaemia, may exacerbate renal injury and create a proinflammatory environment. Oxidative stress is an imbalance of reactive oxygen species [e.g., superoxide (O2-), hydrogen peroxide (H2O2) and hydroxyl radicals (OH)] and antioxidant mechanisms (e.g., superoxide dismutase, catalase, glutathione peroxidase, glutathione, vitamin E) and can also contribute to a proinflammatory environment within the kidney and renal disease progression.

Dogs with CKD showed significantly lower plasma concentrations of vitamin E (alpha-tocopherol)compared with clinically healthy dogs (Lippi et al., 2017). Anti-oxidant dietary supplementation with added vitamins E and C and beta-carotene has shown reduced DNA damage in cats with renal insufficiency (Plantinga et al 2005). Oxidative stress is increased in cats with CKD and it may play a role in renal fibrosis. In cats fed a diet supplemented with the anti-oxidants vitamin E, vitamin C and beta-carotene markers of DNA damage were reduced compared to when they were previously fed a non-supplemented diet.

Probiotics

Live bacteria may be used to catabolize urea and other uremic toxins, thereby effectively trapping them within the lumen of the bowel to be excreted in the faeces. Selected species of probiotic bacteria including*Streptococcus thermophilus, Lactobacillus acidophilus, and Bifidobacteria spp*. in rats with induced CKDdecreased blood concentrations of uremic toxins, altered renal function and prolonged survival time compared to placebo-controls. Some preliminary uncontrolled observational studies using cats and dogs with spontaneous CKD have yielded similar results with both BUN and serum creatinine values declining after initiation of probiotic therapy.

A study evaluating the effects of probiotic VSL#3 (Sivoy) on glomerular filtration rate (GFR) in dogs affected by chronic kidney disease (CKD) showed that supplementation seemed to be efficient in reducing deterioration of GFR over time (Lippi et. al, 2018).

Monitoring

The importance of monitoring cannot be overemphasized. Response to any therapeutic intervention must be carefully assessed both in terms of clinical improvement and impact on disease progression. In addition to standard CKD monitoring (via physical exam, bloodwork, urinalysis, medical history), regular nutritional evaluations (including weight, BCS, muscle mass, food intake, etc.) are important to adjust the plan. Careful owner education and communication improves understanding and compliance with the ultimate goal of improving both quality of life and longevity for their dog or cat.

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