The interrelationship between calcium, phosphorus, parathyroid hormone, activated vitamin D and fibroblast growth factor has a profound impact on the progression of chronic kidney disease (CKD) in dogs and cats. Beneficial effects of calcitriol treatment during CKD have traditionally been attributed to regulation of parathyroid hormone (PTH). New analysis of information emphasize direct renoprotective actions independent of PTH and calcium. It is now apparent that calcitriol exerts an important effect on renal tubular Vitamin D which may be important in maintaining adequate circulating Vitamin D. This in turn may be vital for important actions of Vitamin D on peripheral tissue. Limited information is available reporting the benefit of calcitriol treatment in dogs and cats with CKD. However, a survival benefit has been shown in dogs with CKD treated with calcitriol compared to placebo. The concentrations of circulating Vitamin D have recently been shown to be low in people and dogs with CKD and are related to survival in people. In 2015, there will be compelling data regarding the benefit of calcitriol use in cats with CKD.

Rather than focus on the dearth of evidence for several forms of intervention, this talk will focus on a historic review of the use of dietary therapy, phosphorus binding agents and calcitriol over a ten year period. These are all client-owner cats. Therefore, these are not randomized, blinded, controlled studies. Rather, these cases are a demonstration of practical interventions that have prolonged good quality of life in cats who may not have agreed to all of the recommendations made in the literature.

In assessing renal disease in cats, the most sensitive indicator is the loss of urine concentrating ability. The use of an early morning urine sample to assess urine specific gravity (USG) may help to counter effects of diet or drugs on a tested sample. Using the International Renal Interest Society (IRIS) values for classification of renal disease can be helpful in planning therapy. In some classifications IRIS 2 is divided in to 2a (Cr. 1.6-2.4 mg/dl) and 2b (2.5-2.8 mg/dl). In our practices the classification of 2a with USG less than 1.030 eating a mostly dry diet formula, for example, are started on treatment for chronic progressive renal disease (CPRD). Early intervention prolongs quality of life, good body condition score and wellbeing in a number of key ways. We use ultrasound guided cystocentesis in every cat from whom urine is obtained. This allows a quick early morning visit by the owner, a sterile sample for culture if indicated, a full assessment of the appearance of the urinary bladder and observation of complications such as uroliths.

One of the most frustrating aspects of treating this and any condition requiring lifelong therapy in cats is the difficulty clients have complying with our recommendations. Cats resist contact or intervention they haven’t agreed to and clients want to preserve the relationship they have with their cat, often at the expense of appropriate therapy. It is essential then to choose the most effective forms of therapy, to provide options when resistance is experienced and to communicate a willingness to the client to assist in preserving the relationship they have with their beloved cat.

While it has been shown that dietary modification has the most positive long-term effect on outcome, the relationship between survival and protein restriction or the attendant restriction of phosphorus has yet to be illuminated fully. Strong evidence, however, supports dietary phosphorus restriction in animals with kidney disease. Serum phosphorus is an independent predictor of disease in cats with chronic kidney disease. Cats with induced renal disease fed phosphorus –restricted diets had less severe histological renal changes than cats fed normal diets.

Phosphate retention and hyperphosphatemia are primarily due to impaired renal phosphate excretion. If renal function is normal, clinically significant hyperphosphatemia seldom develops. In the early stages of CPRD increased levels of PTH can keep serum phosphorus within the reference range by decreasing expression of the sodium-phosphate transport system in the proximal tubule resulting in increased urine phosphate excretion. This allows for normalization of serum phosphorus at the expense of hyperparathyroidism.

As cats are quite specific about preferences in taste, texture and flavor, the use of renal formulated diets may not always be possible. Alternatives may not have been thoroughly tested to the extent that prescription diets are but the truth of the statement “It is more important THAT he eats than WHAT he eats” is undeniable. Treatment goals of dietary modification start with maintaining body weight and a normal body condition score. If renal diets are not tolerated, warm canned diets diluted with some form of flavored moisture are a good choice. Other alternatives include adding other forms of moisture to food to increase fluid intake, providing flavored waters to encourage moisture consumption, water fountains and multiple drinking places throughout the house.

If a renal diet is not fed, most cats will tolerate low doses of aluminum hydroxide in food to act as a phosphorus binder, before serum phosphorus levels leave the normal range. Serum phosphorus should remain in the 4-5 mg/dl range, especially if calcitriol is considered. Low body condition scores and malnutrition are negative prognostic indicators in dogs and the same is likely to be true in cats. If adequate caloric intake and preservation of lean body mass does not occur, quality of life will decline.

Studies done to confirm preservation of lean body mass in cats fed a low protein diet, about 28% on an as-fed basis, were, as one would anticipate, time restricted to around 4 months. With the advent of a better plan for managing renal patients, they are living for
years with stable renal values and hematocrits within the normal range. The effects of protein restriction on the body condition scores of cats with CPRD should be evaluated. Until then, we all have observed the protein cachexia of our renal patients. It is crucial to preserve adequate caloric intake and adequate protein for these patients.

The effects of uremia on appetite are well known, particularly in human renal patients. The use of H2 blockers for uremic gastritis can be helpful in encouraging consumption of adequate calories. The use of mirtazapine as an appetite stimulant is helpful in those cats who can tolerate it. We use 1/8 of a 15 mg tablet every day to every third day depending upon response to therapy. Many cats with CPRD are underweight and dosing of 1/3 of a tablet as has been recommended is often followed by restlessness, anxiety and vocalizing in cats who are sensitive to it. Clients can be quite upset by this and may be less inclined to follow other treatment recommendations. Both of these forms of therapy imply being able to accomplish giving fragments of a pill to a cat on a regular basis and over a prolonged period of time. Strategies for this should be included in client education including the use of “sticky” high value food like cheese in a can, cream cheese or pill pockets and other soft treats.

Calcitriol has long been reported to provide benefits to the human uremic patient by lowering parathyroid hormone concentration. This has also been reported in dogs and cats. Oral calcitriol has been shown to increase survival in human patients with CPRD including those treated prior to dialysis. The antiproteinuria effects of Vitamin D analogs are of crucial significance because proteinuria is a major risk factor for the progressive decline of renal function in both dogs and cats. Podocytes are critically important in overall glomerular function and structure. Injury to podocytes commonly leads to proteinuria and glomerulosclerosis. A marker for podocyte injury, desmin, was lowered by calcitriol in one model of CPRD in rats. Fibrosis as either glomerulosclerosis or tubulointerstitial fibrosis is a common sequelae in CPRD. Calcitriol in physiologic doses interfered with glomerular proliferation and growth, lessening glomerulosclerosis in a rat model. Calcitriol treatment of an experimental glomerulonephritis model in rats inhibited medangial cell proliferation, glomerulosclerosis and albuminuria.

The renin-angiotensin-aldosterone system (RAAS) is a major mediator of progressive renal injury in CPRD. The RAAS system is present entirely within the kidney and is present in most renal cells including tubular epithelia.

Calcitriol is a negative endocrine regulator of RAAS. Calcitriol suppresses renin biosynthesis and has a protective role against hyperglycemia-induced renal injury in diabetic human patients. Through its effect to inhibit RAAS, calcitriol decreases production of Angiotensin II and thus lessens these fibrogenic consequences as well as other harmful renal effects.

A glomerular mesangial or interstitial inflammatory reaction with marked involvement of macrophages and lymphocytes attends all forms of renal disease. Together with control of RAAS, the ability of calcitriol to control inflammation are hallmarks of renoprotective actions.

In our practices, early diagnosis of CPRD at the IRIS 2a or b level is the key to successful management. A cat with or without proteinuria, with or without hypertension with a USG less than 1.030 and normal Calcium and Phosphorus will be started on Calcitriol at a dose of 2.5-3.5 ng/Kg per day. This is compounded into a chicken or fish flavored oil base by a compounding pharmacy licensed to produce compounded pharmaceuticals for the human market. Calcium, Phosphorus and their product will be measured in 2 weeks.

While the literature is clear that iCA is a far more accurate measure of total body calcium, it is an expensive test. Our protocol calls for frequent testing of renal values including calcium and phosphorus. We would be treating a fraction of the cats we can help if this costly test were included. Instead we use a protocol advocated by Larry Nagode and Dennis Chew, Pathology and Urology professors respectively at the Ohio State University Veterinary College.

One of the benefits of the preservation of renal tissue using this protocol is the preservation of erythropoietin production and the consequent preservation of normal hematocrits. Cats with IRIS Stage 3-4 CPRD are still feeling better, more active and eating better with adequate circulating red cells. Anemia is a quality of life issue.

Hepcidin excess prevents iron absorption from the diet and blocks iron release from body stores by binding to and inducing the degradation of the iron export protein ferroportin. A mechanism for the EPO sparing effects of vitamin D is suggested by recent data demonstrating a hepcidin lowering effect of vitamin D. In vitro treatment with vitamin D of monocytes isolated from hemodialysis patients downregulated hepcidin transcription. Furthermore, oral administration of vitamin D in healthy volunteers lowered serum levels of hepcidin by 50% compared to baseline levels within 24 hr and persisted for 72 hr. Supplementation with vitamin D has also been reported to have beneficial effects on increasing erythropoiesis and decreasing inflammation. These initial results are promising, and a randomized controlled study is warranted to determine whether correction of vitamin D deficiency can ameliorate ACD.

References
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