What Is Different About Chronic Kidney Disease in Cats?

David J. Polzin, DVM, PhD DACVIM

Professor, University of Minnesota
College of Veterinary Medicine
St. Paul, MN
Introduction

Kidney disease is defined as the presence of functional or structural abnormalities in one or both kidneys. (CKD) is defined as kidney disease that has existed for at least three months. Chronic kidney disease is the most common kidney disease in cats. As in most species, CKD is primarily a disease of aged cats. The prevalence of CKD among cats of all ages has been estimated to be 112 cases per 1000 cats examined. Among cats 10 years of age and older, the prevalence was 269 per 1000 cats examined, while the prevalence among cats 15 years of age and older was 491 per 1000 cats examined. The prevalence of CKD in cats appears to be approximately two to three times greater than in dogs. The reason for the unusually high prevalence of CKD in cats compared to dogs is unknown. Although CKD is an irreversible and progressive condition, most cats with CKD survive for many months to years. Many of these cats ultimately die of conditions other than CKD.

Recognition and Staging of Chronic Kidney Disease in Cats

Although CKD may initially be recognized as abnormalities detected by physical examination, serum biochemistries, urinalysis or imaging studies, it is most commonly detected as reduced renal function (azotemia). Differentiating renal azotemia from prerenal azotemia is usually based on examining urine concentration concurrent with detection of azotemia. Since cats tend to have exceptional ability to concentrate their urine, it is not surprising that, compared to dogs or humans, cats typically maintain a greater degree of urine concentrating ability as renal function declines. As a consequence, less advanced CKD may be associated with relatively concentrated urine in some cats. Absent other causes for dilute urine (e.g. hyperthyroidism, diabetes mellitus, etc.), serum creatinine values of 1.6 mg/dl or greater associated with urine specific gravity values less than 1.035 should generally be interpreted as consistent with renal azotemia. Cats with more advanced CKD typically have urine specific gravity values below 1.020. Urine specific gravity values between 1.035 and 1.040 constitute a “grey zone” where azotemia may be renal or prerenal. However, the occasional cat may present a diagnostic dilemma in that they remain persistently azotemic for months to years with urine specific gravity values greater than 1.040. These cats most likely have CKD.

To facilitate application of appropriate clinical practice guidelines for diagnosis and treatment, patients with chronic kidney disease are categorized into four stages along a continuum of progressive kidney disease. The stage of CKD is assigned based on the level of kidney function as determined by two or more determinations of serum creatinine concentration obtained while the patient is well hydrated. Cats with CKD having stable serum creatinine values less than 1.6 mg/dl are classified as stage 1 CKD. Cats with CKD having stable serum creatinine values between 1.6 mg/dl and 2.8 mg/dl, between 2.9 mg/dl and 5.0 mg/dl and greater than 5.0 mg/dl are classified as stages 2, 3, and 4, respectively. The stage is further modified by proteinuria status and blood pressure. Cats with urine protein:creatinine ratios less than 0.2 classified as non-proteinuria, ratios between 0.2 and 0.4 as borderline proteinuria and cats with ratios greater than 0.4 are considered proteinuric. Cats with systolic blood pressure values less than 150 mmHg are considered as having minimal risk of experiencing hypertensive end-organ injuries (e.g. renal, ocular, cardiac or nervous system lesions). Cats with systolic blood pressure values between 150 mmHg and 159 mmHg, 160 mmHg and 179 mmHg, or greater than 180 mmHg are considered as having low, moderate or high risk of experiencing hypertensive end-organ injuries. The stages of CKD are modified by their magnitude of proteinuria and systemic hypertension because these factors appear to influence prognosis and are amenable to therapeutic modification.

Etiology and Pathology of Feline Chronic Kidney Disease

Chronic kidney disease in cats may be initiated by a variety of different familial, congenital, or acquired diseases. Unfortunately, the initiating cause(s) of CKD often cannot be identified at the time of diagnosis. In one study, chronic tubulointerstitial nephritis was observed in 70% of cats with CKD,
while glomerulonephropathy occurred in 15%, and lymphoma in 11%, amyloidosis in 2%, and tubulonephrosis in 2%. The prevalence of non-proteinuric tubulointerstitial disease appears to be greater in cats compared to dogs or humans. Unfortunately the histological diagnosis of tubulointerstitial nephritis does not aid in the identification of the underlying etiology of the kidney disease, and probably represents the final common pathway for progression of many feline renal diseases. The initiating causes of diseases thought to originate in the tubulointerstitium have been especially elusive. However, one possible cause for the higher prevalence of CKD in cats has recently been proposed. Subcutaneous administration of feline herpesvirus 1, calicivirus, and panleukopenia virus vaccines grown in feline tissue culture systems to kittens have been shown to induce production of anti-feline renal tissue antibodies in serum and a tubulointerstitial inflammatory response within the renal tubulointerstitium. This observation prompts the question as to whether repeated vaccinations play a role in development of CKD in cats.

An additional interesting observation that appears to be unique to cats is the high frequency of nephroliths and ureteroliths in cats with CKD. These uroliths are predominantly composed of calcium oxalate. The origin of these uroliths and whether or not the uroliths develop before, during or after the onset of CKD are not known. Although ureteroliths have become an important cause for acute uremic crises in cats, the presence of nephroliths does not appear to adversely affect clinical outcomes in cats with CKD. Although it may be necessary to surgically remove ureteroliths associated with complete, persistent ureteral obstruction, removal of nephroliths is generally not recommended.

**Biological Behavior of Feline Chronic Kidney Disease**

A progressive decline in kidney function over months to years is typical of naturally occurring CKD. While logical to assume that CKD progresses as a consequence of ongoing renal injury associated with the disease process that initiated CRF, the initiating cause for CKD cannot be identified at the time of diagnosis in most patients. The preponderance of clinical and experimental evidence suggest that in dogs and cats with stages 3 and 4 CKD, progressive loss of kidney function results, at least in part, from factors unrelated to the inciting disease. These factors may include intraglomerular hypertension, glomerular hypertrophy, hypertension, proteinuria, intrarenal precipitation of calcium phosphate and tubulointerstitial disease.

While progression of CKD in humans and dogs is often characterized by a linear pattern of decline in GFR, progression of CKD in cats more commonly appears as abrupt, usually unpredictable increases in serum creatinine concentration. In a recent clinical trial at the University of Minnesota, renal function as measured by serum creatinine was found to remain stable for up to 24 months in 40 of 45 cats. Five of the 45 cats developed uremic crises associated with abrupt increases in serum creatinine concentrations after having had stable renal function for 3 to 21 months. Upon retrospective evaluation of the clinical data on these cats, no clear indicators were found to be useful in predicting an impending decline in kidney function.

The seeming stability of renal function in many cats with CKD translates into relatively long survival time. Compared to dogs with similar levels of renal dysfunction, cats typically live many months or years longer. In fact, many older cats with CKD succumb to other diseases before their CKD becomes severe enough to cause significant morbidity.

**Modifying Clinical Outcomes in Cats with Chronic Kidney Disease**

Even though feline CKD tends to be generally less progressive than CKD in dogs, many cats nonetheless progress to a point where they become difficult or impossible to manage with a satisfactory quality of life. Recent studies have indicated that certain medical interventions may delay or prevent progression of CKD, thereby extending survival with a good quality of life. Factors that have been shown to influence survival times for cats with CKD include the severity of reduction in GFR (stage of CKD) and magnitude of proteinuria. There may also be an interaction between systemic hypertension and proteinuria on survival. With greater severity of intrinsic renal dysfunction and/or magnitude of proteinuria, shorter survival time is likely. Some other factors that may or may not
influence progression of CKD directly include systemic hypertension, pyelonephritis, and presence of nephroliths.

All patients with CKD are potentially at risk for progressive kidney disease. Progression may occur as a consequence of their primary renal disease, in association with a variety of secondary factors that may promote progressive renal disease, or both. An important therapeutic goal for managing patients with CKD is to minimize or prevent progressive loss of renal function. Treatment designed to limit progression of kidney disease may involve a variety of interventions including diet therapy, minimizing proteinuria, controlling hypertension, and modulating the renin-angiotensin-aldosterone system.

There is substantial clinical trial evidence supporting the effectiveness of dietary intervention in prolonging survival of cats with CKD; there is no credible clinical evidence to the contrary. In a non-randomized clinical trial, cats fed a renal diet survived significantly longer than cats that continued to consume their usual diet (633 days versus 264 days). It was not possible to detail the differences between diets used in this study, but the therapeutic renal diet was reduced in protein and phosphorus content. The renal diet was shown to be beneficial in lowering serum phosphorus and PTH concentrations, and it was suggested that the beneficial effect of the diet may have been related to this effect. A recently published randomized, controlled clinical trial further from the University of Minnesota veterinary Medical Center confirmed the beneficial effects of diet therapy in prolonging survival of CKD in cats. In this study, the effect of a renal diet was compared to a maintenance diet on survival in 45 cats with spontaneous CKD. Renal-related mortality in 23 cats fed an adult maintenance diet was 17.4%, while no deaths were observed in 22 cats fed the renal diet which was restricted in protein and phosphorous content. In a retrospective study of cats with CKD treated at 31 veterinary clinics in The Netherlands, feeding a “renal diet” compared to a typical feline diet was found to be associated with a significant increase in median survival time (7 months among cats consuming conventional cat foods and 16 months for cats consuming a renal diet).

A common misconception is that renal diets are simply “low protein diets.” Renal diets encompass a variety of modifications beyond just a limitation of protein content, and, indeed, the principal beneficial effects of these diets may not accrue from their reduction in protein content. Thus, simply replacing a renal diet with a standard manufactured diet that is lower in protein content does not meet the guideline of feeding a renal diet. Since inappropriate diets can exacerbate clinical signs of uremia and/or promote progression of CKD, cats with CKD should be fed a renal diet.

Treatments designed to reduce glomerular proteinuria are recommended for managing proteinuric cats with CKD stages 1 through 4. Intervention is indicated when the urine protein-to-creatinine ratio (UPC) exceeds 2.0 in cats with CKD stage 1, and when the UPC exceeds 0.4 in cats with CKD stages 2 through 4. Proteinuria has been shown to adversely affect outcomes in humans, dogs and cats with CKD, presumably because proteinuria itself appears to injure the renal tubules, thereby promoting progression of CKD. It is well established in human patients that reducing proteinuria by suppressing the renin-angiotensin-aldosterone system ameliorates the adverse effects of proteinuria on the kidneys. Although qualitatively similar, evidence in cats is less compelling. Although studies have shown that proteinuria is closely linked to progression of CKD in cats and that ACE inhibitors are effective in reducing proteinuria in cats with CKD, the effectiveness of ACE inhibitor therapy in altering the course of CKD cats remains to be confirmed. Nonetheless, ACE inhibitors such as benazepril and enalapril are recommended for CKD patients that meet the above criteria. Interestingly, treatment of systemic hypertension in cats with CKD using amlodipine besylate has been shown to be associated with a reduction in the magnitude of proteinuria. Ideally, therapy should be adjusted such that the urine protein:creatinine ratio is reduced to 0.4 or lower. However, this may be difficult in some patients and may require higher doses of the ACE inhibitors or the addition of angiotensin II receptor blocking drugs (e.g. losartan or irbesartan).
References


