Literature Review – Epidemiology of Feline Chronic Kidney Disease

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INTRODUCTION

Chronic kidney disease (CKD), also referred to as chronic renal failure, is one of the most common causes of illness and death in geriatric cats.[1] CKD was diagnosed in 1.5 percent of all Banfield feline patients seen in 2010 (n = 444,419); it was most common in cats ≥ 10 years of age (7.5 percent [5,498/73,396]). Of the cats diagnosed with CKD, those ≥ 10 years of age constituted the largest proportion of cats with CKD (81 percent), followed by mature adults (≥ 3 years but < 10 years of age) at 17 percent. The overall prevalence is slightly higher than that reported for a retrospective study[2] of cats seen at teaching hospitals (1.2 percent [2,228/189,371] between 1980 and 1990). In that study, only 63 percent of affected cats were geriatric. However, both sets of data concur with other findings that, despite the occasional diagnosis of CKD in kittens < 6 months of age (Banfield data), CKD is primarily an age-related disease.[2-4]

The prevalence of CKD appears to be increasing. The aforementioned teaching hospital study[2] revealed the period prevalence increased from 0.4 percent to 1.6 percent between 1980 and 1990. These cats were more likely to be taken to the hospital because of illness rather than for preventive healthcare, and rates were not adjusted to account for

the difference in patient age distribution during the same period. At Banfield hospitals, where patients may be more representative of the general pet feline population, the age-adjusted prevalence increased from 0.8 percent (79 cases per 10,000 cats seen) in 2006 to 1.6 percent (160 cases per 10,000) so far in 2011 (Banfield data; *Figure 1,* page 2).

CLINICAL BOTTOM LINE

- Chronic kidney disease (CKD) is a common cause of illness and death in aging cats.

- Middle-aged and, in particular, geriatric cats are most at risk.

- Early detection and treatment may lead to a longer period without clinical signs and a longer life in affected cats.

- No single diagnostic test exists for CKD detection.

- More information is needed on how serum creatinine concentration or other blood and urine analytes might be used to reliably detect CKD in its early stages.

- The best method for CKD detection remains regular physical examination, history taking and routine, serial clinicopathologic testing.

Figure 1. Age-adjusted Prevalence of CKD in Feline Patients Seen at Banfield Hospitals, January 2006 through August 2011
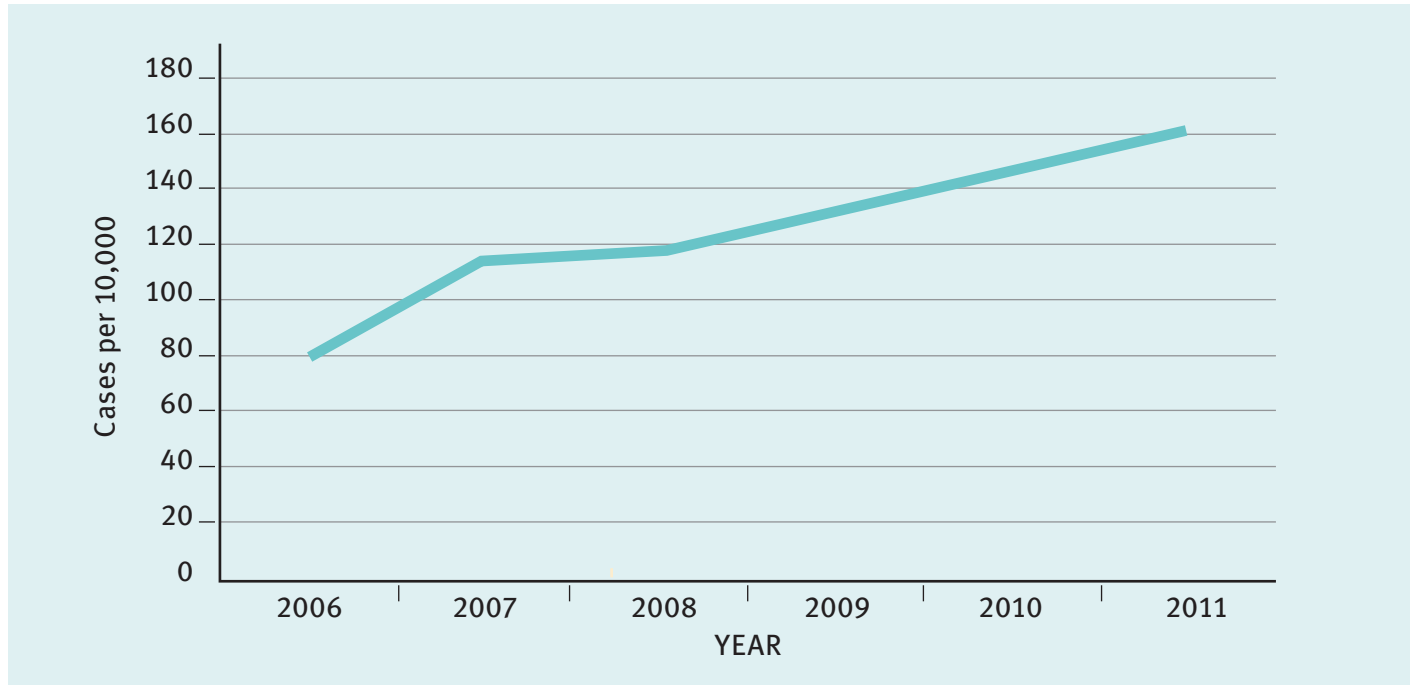
Chronic kidney disease can be attributed to multiple etiologies. Chronic dysfunction may be caused by congenital problems such as polycystic kidney disease or renal dysplasia, by glomerulonephritis secondary to certain acquired systemic conditions such as neoplasia or infection, or by an unidentified process. In this report, the last and most common of these types of chronic disease—idiopathic CKD[2,3]—will be discussed.

The irreversible loss of kidney function in cats with CKD makes the disease a serious problem in feline medicine. Although not all types of idiopathic CKD are progressive, many types are;[5] yet the difference between cats with progressive disease and those without it remains unclear. The clinical signs of CKD such as polyuria/polydipsia, inappetance and weight loss are primarily attributable to the severely reduced capacity of the kidneys to filter waste products out of the blood and to regulate electrolyte balances within the body,[6,7] *i.e.*, a severe reduction in glomerular filtration rate (GFR) through tubulointerstitial damage. Although it is often cited that kidneys are capable of adequate filtration until a certain threshold of loss is met (*e.g.*, loss of 75-80 percent of renal nephrons), experimental evidence involving induced CKD through surgical reduction of renal mass suggests the cutoff may not be so sharply defined.[8] Regardless of the exact amount of damage needed before the clinical signs of CKD become noticeable, by the time the disease is diagnosed, the damage is already severe, with significant loss of kidney function. Because the pathologic changes in CKD are permanent, treatment of affected cats is aimed at reducing the filtration load on the remaining functional portion of the kidneys, ameliorating clinical signs, and slowing disease progression if possible.
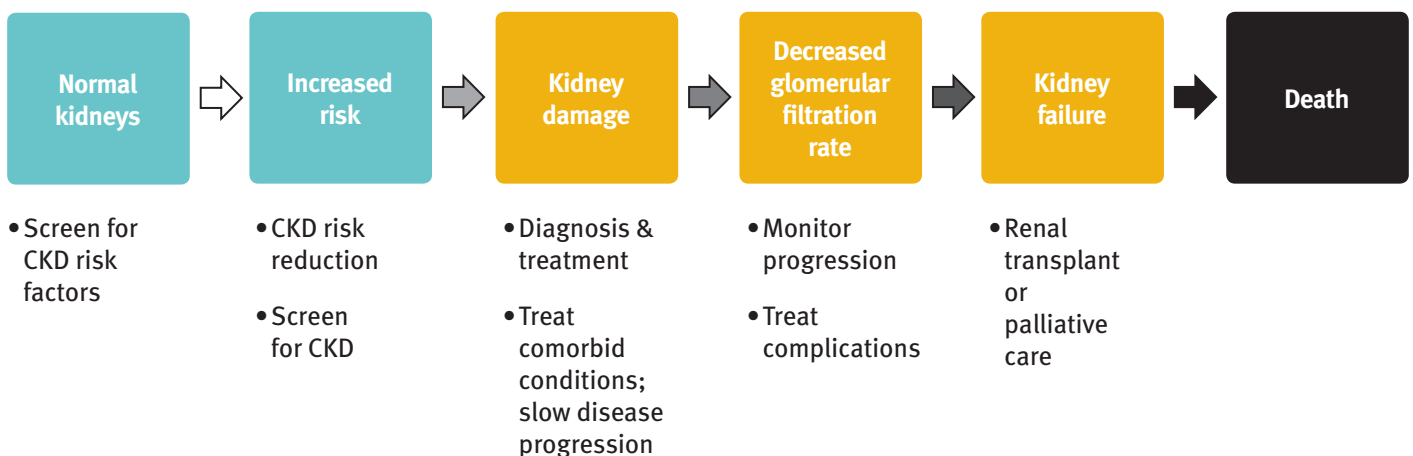
SCREENING OF CATS FOR CKD RISK FACTORS

The high prevalence of CKD in aging cats and its potentially devastating impact on affected pets and their owners justifies recommendation of annual to semi-annual health examinations and blood work for all middle-aged and geriatric cats. Basic screening for CKD includes both history-taking and laboratory tests. The National Kidney Foundation has developed an "evidence model" that summarizes the progression of CKD with respect to points of screening and potential intervention (*Figure 2*).[9] Although designed for use in human medicine, the model can be applied in veterinary settings. When translated for feline medicine, the recommendation is that when cats are healthy, they should be screened for CKD on the basis of risk factors. Cats in which risk factors are identified can then be screened for CKD with specific tests.

In human medicine, risk factors for CKD have been grouped into four categories.[9] Susceptibility factors include those that increase a patient's risk of developing CKD. Because such factors can be useful in screening for CKD in cats, they will be discussed here. Initiation factors (white arrow in *Figure 2*) are those that can directly cause kidney damage, which are largely unknown in idiopathic CKD. An example in cats might include age, which would place older cats in the increased-risk stage. Factors that cause kidney damage to progress (gray arrows) would include conditions to which the kidneys are exposed once the disease process begins. Finally, end-stage factors (black arrow) are those that increase the severity of illness, with death as the final outcome. Cats are often diagnosed with CKD when the disease has already progressed to a state that would be classified as "end-stage" in human medicine, so late referral or detection could be considered an end-stage factor in cats.

Not much can be done about end-stage factors in cats other than euthanasia, so the aim in veterinary medicine is to address factors that increase the risk of developing CKD and factors that influence progression of the disease. Surprisingly little work has been done to identify risk factors for CKD development in cats. Although direct causes such as pyelonephritis[10] may be readily identified in some situations, factors contributing to idiopathic CKD are nebulous, likely

Figure 2. Evidence Model for the Development and Treatment of Chronic Kidney Disease (CKD) in Cats

Normal kidneys	Increased risk	Kidney damage	Decreased glomerular filtration rate	Kidney failure	Death
• Screen for CKD risk factors	• CKD risk reduction • Screen for CKD	• Diagnosis & treatment • Treat comorbid conditions; slow disease progression	• Monitor progression • Treat complications	• Renal transplant or palliative care	

because of the difficulty distinguishing risk factors from concurrent disease processes also associated with aging. Distinguishing risk factors for CKD is complicated by the fact that cats are often diagnosed at the end-stage of the disease process, by which time the severity of histopathologic renal changes obscures identification of the inciting cause.[1] Indeed, it is likely that multiple factors contribute to the gradual decline in renal function over time and that concurrent diseases exacerbate this decline.

Cat breed is one possible risk factor. The prevalence of CKD in Maine Coon, Abyssinian, Siamese, Russian Blue, and Burmese cats in one retrospective study[2] was twice as high as the average prevalence in all feline patients (n = 189,371) at 23 veterinary teaching hospitals from 1980 through 1990. There is no mention of whether diseases with known breed predispositions such as polycystic kidney disease and amyloidosis were included in the definition of CKD. Consequently, one cannot be assured that the breed influence identified is relevant to idiopathic CKD. Another study[3] failed to reveal an association between CKD and breed; however, only 74 cats were included, thereby limiting the power to detect any association. Interestingly, there appears to be a significant ($P < 0.001$) effect of cat breed on creatinine values in healthy, fasted cats, which might reflect a breed predisposition for CKD[11] or other renal disease. However, the specific breeds contributing to that effect is unknown.

Cat sex is another putative risk factor that has received attention. Some evidence suggests male cats may be at risk of developing CKD earlier than female cats. In a prospective case series of 184 Australian cats with CKD, the median age of male cats was 12 years, whereas that of female cats was 15 years.[4] Other findings[12] suggest males have higher creatinine values than females so, for example, if a creatinine concentration of 1.6 μg/dL is used as a laboratory diagnosis of CKD, then males would be expected to reach that concentration sooner than females would.

Diet type has long been suspected to play a role in the development of CKD. Type of diet (*e.g.,* dry, canned or pouch cat food or table scraps) was not found to be associated with CKD development in one study.[13] However, these results were obtained through univariate analyses, without controlling for other factors that could obscure any association that might exist.

Diet nutrient composition has also been investigated for an association with CKD. Potassium and protein content have been identified as two important components. In a case series in which nine healthy adult cats were fed a high-protein (41 percent of dry matter) commercial diet with low potassium content (0.5 percent) for 65 weeks, three eventually developed clinical signs and clinicopathologic changes characteristic of CKD.[14] That said, restriction of dietary protein intake in cats that already have CKD remains controversial. One study[8] revealed that nephrectomized cats that consumed a high-protein, high-calorie diet for a year developed considerable morphologic injury in the remaining kidney tissue, whereas those that consumed a low-protein, low-calorie diet did not. However, another study[15] showed that the degree of protein and calorie consumption had no effect on glomerular lesions after similar nephrectomies.

It is difficult to differentiate between the effects of reducing the amount of protein and phosphorus (a

component of many proteins) in diets because these effects are often investigated simultaneously. For example, a randomized controlled trial (RCT)[16] found that cats with CKD fed a diet with restricted protein and phosphorus content had a mean weight gain (versus loss) and mean decrease (versus increase) in serum urea nitrogen and creatinine concentrations over a 24-week period, compared with cats fed a control diet. Results of other dietary trials[17,18] (one randomized and one nonrandomized) in cats with naturally occurring CKD and two others in cats with experimentally induced disease[8,19] support the hypothesis that diets low in protein and/or phosphorus content can not only ameliorate some of the clinical signs associated with CKD but may also indeed slow the progression of renal damage.

Even the quantity of diet consumed may be linked to CKD in cats. In a questionnaire-based, case-control study,[20] cat diet and lifestyle factors were evaluated as putative risk factors for CKD. Although the sample size was small (38 cats with CKD and 56 healthy cats) and the control cats had not been screened for CKD specifically, the study did find that cats with CKD were four times as likely to have had *ad libitum* access to food as were healthy cats (95 percent confidence interval, 1.1 to 15.8). The authors claimed that increased dietary fiber intake in various combinations was associated with decreased odds of CKD; however, the reported confidence intervals, which included 1, suggested that association was nonsignificant.

Determining whether certain diseases increase the risk of cats developing CKD has proven difficult. Whether hypertension is a risk factor for or results from CKD is debatable; it is possible both are true. Some report, without evidence, that hypertension

may lead to CKD in cats[21] or that hypertension may directly cause CKD.[22] On the other hand, in cats with experimentally reduced renal mass, blood pressure was significantly higher than in control cats, suggesting hypertension was a sequel to CKD.[8] In Banfield patients in 2010, hypertension was diagnosed in 52 of 6,747 (0.8 percent) cats before a diagnosis of CKD and in 141 (2.1 percent) cats after diagnosis. An extensive critical review of other evidence regarding hypertension and CKD in companion animals is available elsewhere.[23]

Cats with CKD often have concurrent hyper-thyroidism.[4] Hyperthyroidism, which increases blood flow to the kidneys, can mask the signs of CKD, but it has not been established that hyperthyroidism can cause CKD. A case-control study[13] (n = 92 cats/group) in which univariate analysis was performed failed to find that hyperthyroidism in the past predicted future diagnosis of CKD. However, that study's validity is questionable given that it relied on owner reports rather than veterinary records for data on putative risk factors for CKD.

Periodontal disease has been found to be associated with CKD in dogs,[24] with the severity of periodontal disease increasing with severity of CKD. A similar report for cats has not been published, and whether periodontal disease causes CKD remains to be demonstrated in both dogs and cats. Additional research is needed to better define the relationship in companion animals.

If specific infectious causes of CKD could be identified, then prevention might be possible, provided that the cause(s) could be avoided or controlled. Infection with *Leptospira* spp, which have a predilection for

the kidneys, is a condition known to cause CKD under certain conditions but as yet no vaccine is available for cats.[10] Pathogens not commonly considered as agents of renal damage have also been evaluated as potential causes of CKD. Feline immunodeficiency virus (FIV) is one such pathogen. Although one study[25] found an association between FIV infection and CKD, the researchers were unable to show whether the FIV infection preceded development of CKD in the case-control study design. Another study[26] found deposits of immune complexes in kidneys from FIV-infected cats, and researchers concluded these immune complexes may underlie the pathogenesis of CKD in FIV-infected cats; however, no attempt was made to determine whether the same complexes could be found in kidneys from uninfected cats. Infections with the intracellular parasites *Encephalitozoon cuniculi* and *Toxoplasma gondii* were recently found to be unlikely risk factors for CKD in a parochial serologic study of cats with (n = 36) and without (196) CKD.[27]

The question exists whether idiopathic CKD is simply attributable to the aging process in cats. In a retrospective cohort study[28] involving complete records of 600 adult colony cats that had died or were euthanized over a 22-year period, the cats that had succumbed to CKD (histopathologically confirmed progressive renal tubule loss and peritubular interstitial fibrosis) lived longer than those that died from other causes. A colony cat population may be poorly representative of the general pet cat population, but this would not invalidate the investigators' conclusion that the loss of renal tubules appears to be a normal part of aging in cats in the same way that graying of fur or loss of skin elasticity are. They suggest that the kidney damage associated with idiopathic CKD actually

begins early in life, without an identifiable inciting cause, and is a "survival-driven adaptive process" in that the energy associated with maintaining kidney function is diverted to other, biologically more important processes.
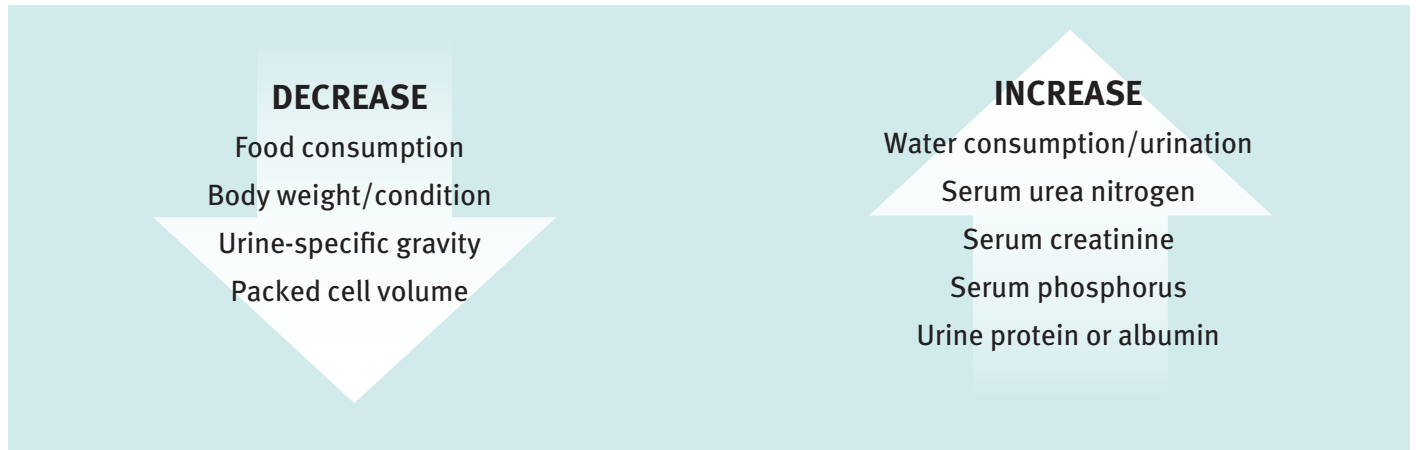
SCREENING OF CATS FOR CKD
Annual to semi-annual comprehensive examinations that include full blood work and urinalysis remain one of the best means for detecting CKD and are highly recommended for cats 8 years of age and older.[10] Screening for CKD in cats is complicated by the fact that clinical signs of CKD—factors that owners would likely notice and report if asked, such as an increase in water consumption or urination—are subtle and nonspecific to the disease.[13] In addition, cats in the early stages of CKD generally will not have any obvious hematologic or serum biochemical abnormalities.[1] As their feline patients age, veterinarians should heighten their vigilance for changes from values in previously performed serum biochemical and CBC profiles. A typical pattern of comprehensive examination findings in cats with early-stage CKD is given in *Figure 3,* page 7.

The ideal test of renal function would allow identification of CKD in its early stages. Several options have been suggested, with none proving specific enough to rule out CKD or sensitive enough to diagnose the disease with certainty, particularly when used alone.

Of the available tests, change in serum creatinine concentration, when measured on an annual or semi-annual basis, probably has the most potential as a screening test, particularly when results are taken in concert with the entire clinical picture (*i.e.,* clinical

Figure 3. Changes in Cats Suggestive of CKD That Can be Detected at Routine Comprehensive Examinations

DECREASE

Food consumption
Body weight/condition
Urine-specific gravity
Packed cell volume

INCREASE

Water consumption/urination
Serum urea nitrogen
Serum creatinine
Serum phosphorus
Urine protein or albumin

signs and other findings). Because an increase in serum creatinine concentration can result from dehydration and other conditions, such an increase is not pathognomonic for CKD, but a persistent increase over time is.[10] Monitoring of creatinine values seems like it would be a practical, straightforward screening method. However, reference limits for serum or plasma creatinine concentration can vary among laboratories, and may be influenced by the biochemical analyzer used or the characteristics of the subjects sampled in value determinations (*e.g.*, cat numbers, ages or feeding status). For these and other reasons, published reference ranges for healthy cats are believed to be too broad.[29] A commonly used reference text reports the normal creatinine range for cats is 0.5 to 1.9 mg/dL (49 to 165 µmol/L),[30] however this range is more restricted than that of large commercial laboratories (*e.g.*, Antech, 0.6 to 2.5 mg/dL). Given the uncertainty inherent to these reference ranges, determining whether a cat with a value at the upper end of a range is headed toward renal failure is challenging, particularly when considering that the International Renal Interest Society (IRIS) uses a range of 1.6 to 2.8 mg/dL as indicating stage 2 CKD in

diagnosed cats (*Table 1,* page 9). Clearly, 1.6 mg/dL is within all of the aforementioned "normal" ranges. At present, there is no information on the degree of change in creatinine concentration (and other analytes) that can be expected throughout the lifespan of a healthy cat.

Other clinicopathologic tests have also been suggested as being useful in the early detection of CKD. Of these, the most important is urine-specific gravity (USG), which, when < 1.035 and when concurrently measured serum creatinine concentration is > 1.6 mg/dL, is a good indication that kidney disease is present.[29] Consequently, measurements of USG and serum urea nitrogen concentration are useful adjuncts in CKD screening and diagnosis and are also components of the IRIS staging schema. Although some cats with stage 2 or later CKD may retain urine concentrating ability (urine specific gravity values > 1.040), their USG values will progressively decrease with disease progression.[5,31]

The persistence of protein and/or albumin in urine from one examination to the next may identify CKD

before a cat becomes azotemic.[10] Detection of a urine albumin concentration that is greater than normal but less than the lower detection limit of standard urine assays (microalbuminuria) has been proposed as a potential method for early detection of CKD in cats.[10] At this point, available assays lack the sensitivity to be used as screening tests for CKD, and they do not appear to be specific to CKD.[32] Because proteinuria and albuminuria are common to other diseases and physiologic processes,[32,33] veterinarians should keep in mind that the presence of protein or albumin in urine is not enough to confirm CKD on its own. That said, determination of the urine protein-to-creatinine ratio (UP:C) or urine albumin-to-creatinine ratio (UA:C) has been recommended to assess not only the presence of CKD but the prognosis in affected cats,[5] with lower UP:Cs or UA:Cs predicting a better prognosis.[34] In a study[35] involving cats with naturally acquired renal failure, those with a UP:C < 0.43 survived a median of 766 days after diagnosis, whereas cats with a UP:C > 0.43 survived a median of 281 days. As with creatinine concentration, the cutoffs used for UP:C ratios in that study may not pertain to all cats (*e.g.*, neutered male cats).

Urinary retinol binding protein has been proposed as a potential analyte for early detection of CKD;[36] however, information on the sensitivity and specificity of an immunoassay for the protein is lacking, so its use is not recommended at this point. Other tests are aimed at measuring GFR for direct detection of reduced renal function prior to onset of azotemia, but are more suitable for use as screening tests in high-risk cats such as those with heritable renal diseases. Of the clinically practical tests, plasma iohexol clearance has been evaluated against exogenous creatinine clearance in cats with

healthy and nephrectomized kidneys, showing a strong association between results of the two tests ($r = 0.951$);[37] however, the reliability of exogenous creatinine clearance as an estimation of GFR is reportedly low.[38] Another study revealed differences in GFR estimates when plasma endo- and exo-iohexol clearances and exogenous creatinine clearance were compared in cats of various health states.[39]

RISK FACTORS FOR DISEASE PROGRESSION

A model for predicting progression of CKD to kidney failure (defined as the need for dialysis or transplantation) has been developed in human medicine and includes such factors as age, sex, GFR and various serum analytes.[40] In veterinary medicine, our understanding of risk factors for disease progression lags far behind and the weighting of each in disease prediction is unknown. What is known is that proteinuria and UPC are correlated with a decrease in survival time in cats with CKD;[35,41,42] and with progression of CKD.[33]

Besides the possible contribution of control of dietary protein and phosphorus on the progression of CKD, other nutritional factors evaluated for an influence on disease progression include sodium chloride content, which has been hypothesized to contribute to hypertension in affected cats. In a controlled trial,[43] adult cats with various types of experimentally induced renal damage were fed three diets that varied solely with respect to sodium chloride content (50, 100 or 200 mg of Na/kg of diet). Low sodium (and not high sodium) intake in that study was associated with abnormally high urine potassium concentration and a reduction in GFR, without any apparent beneficial effect on hypertension. Dietary fatty acid content was a

subject of investigation several years ago,[44] and no clear effect has yet been established, whether favorable or adverse.

IRIS uses serum creatinine concentration to classify the progressive stages of CKD (*Table 1*). Each stage can be further divided into sub-stages on the basis of degree of proteinuria (defined as UP:C > 0.4) and/or hypertension. The hypertension sub-stage includes degree of risk of end organ damage (minimal risk when < 10 mm Hg above the upper reference limit; high risk when ≥ 40 mm Hg above that limit).

Staging aids in determining the appropriate treatment, monitoring and prognosis for affected cats. The IRIS stages of CKD also predict how long an affected cat will survive after diagnosis, with later stages strongly associated with shorter survival times.[45] More information on the staging system is available online.[46]

Nephrolithiasis was once hypothesized to influence disease progression. However, a small retrospective case-control study[47] involving cats with IRIS stages 2 or 3 CKD with (n = 7) and without (n = 7) nephroliths revealed that nephroliths had no impact on rate

Table 1. International Renal Interest Society (IRIS) Classification System for Staging CKD in Cats on the Basis of Creatinine Values

Stage	Serum creatinine µg/dL (µmol/L)	Comments
—	‹ 1.6 (‹ 140)	**At risk for CKD** Cats with risk factors for CKD should be regularly screened.
1	‹ 1.6 (‹ 140)	**Non-azotemic** Some renal abnormality other than azotemia is present, such as abnormal findings of renal imaging or palpation or progressively increasing creatinine concentration.
2	1.6–2.8 (140–249)	**Mild renal azotemia*** Clinical signs are typically mild or absent.
3	2.9–5.0 (250–439)	**Moderate renal azotemia** Systemic clinical signs may be present.
4	› 5.0 (› 440)	**Severe renal azotemia** Systemic clinical signs are usually present.

* According to IRIS, cats with mild renal azotemia typically have biochemical values within reference limits but because of the insensitivity of creatinine concentration as a screening test, cats with creatinine values close to the upper reference limit often have renal disease.[46]
— Not applicable

of disease progression, incidence of uremic crises or death. But because of the small sample size, the statistical analysis performed likely had insufficient power to find a difference if one existed. No power analysis was included in study results.

CONCLUSION

Chronic kidney disease is a progressive and irreversible disease that is common in middle-aged and geriatric cats. The earlier CKD is detected, the more easily it can be managed, thereby improving quality of life and prolonging the survival of an affected pet. No single diagnostic test exists for CKD detection. The disease should be suspected when cats have a history of polyuria/polydipsia, inappetance, weight loss and other signs of uremia. Biochemical analysis of blood and urine should be followed up by radiography, ultrasonography and/or renal biopsy if additional evidence is needed to confirm CKD.[10] Early detection of CKD, while ideal, is not simple. Until highly sensitive tests are designed and risk factors have been more clearly established, the best method of detection remains regular physical examination, thorough history-taking and routine, serial clinicopathologic tests.

ABOUT THE AUTHOR

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